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A TEXT-BOOK OF MEDICINE

By AMERICAN AUTHORS

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PREFACE

The rapid growth of medical science during the last few years has made it almost impossible for a single individual to master the entire field. In internal medicine, as in other branches of human knowledge, the age of specialism has of necessity arrived, and some of our ablest practitioners even devote themselves in great measure to one disease. In order that physicians and students of medicine might have the benefit of an authoritative and up-to-date treatise on every medical subject, it seemed desirable to prepare a text-book of medicine in which each disease, or group of diseases, would be discussed by a writer particularly interested in that subject. This book represents an effort to carry out such a plan. In all there are one hundred and thirty contributors, each of whom is a student or investigator of the subject upon which he has written.

Most of the contributors to this book are teachers of medicine in university medical colleges, and have, therefore, presented their material in a form especially acceptable to medical students.

The editor wishes to express his deep appreciation of the whole-hearted coöperation and assistance which have been rendered him by the contributors. He is particularly indebted to his colleague, Dr. Foster Kennedy, the associate editor of the section on Diseases of the Nervous System, whose services have been invaluable in the editing of this important division of internal medicine. Acknowledgment is also due to Miss Martha Taylor of Boston for her very able assistance in editing the manuscripts.

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A TEXT-BOOK OF MEDICINE

BY

AMERICAN AUTHORS

THE INFECTIOUS DISEASES

THE COMMON COLD

(Acute Coryza)

Definition.—The common cold, or acute coryza, is a catarrhal inflammation of the upper respiratory tract which results from infection by micro-organisms, and perhaps from other causes not yet definitely determined. Such terms as "acute rhinitis," "acute pharyngitis," "acute laryngitis," or "tracheitis" are often employed to designate the region chiefly affected by the disease.

Etiology.—The communicability of many catarrhal diseases of the upper respiratory tract strongly suggests that they are infectious in nature, but careful bacteriological investigation has failed to demonstrate a single specific causative agent. Cultures of the nasopharyngeal secretions from patients with colds usually contain organisms indistinguishable from those found in the nose and throat of normal individuals. The commonest of these are various strains of *Staphylococcus*, *Streptococcus*, *Pneumococcus*, *Micrococcus catarrhalis*, *influenza bacillus*, and certain Gram-positive bacilli.

Some of these bacteria under suitable conditions can invade the mucous membranes and give rise to catarrhal symptoms, but their etiological relationship to the common cold has not been satisfactorily determined. It is not uncommon to find very few organisms present during the acute phase of a cold. In fact, they may be so sparse that plate cultures are entirely negative. This suggests that during the early stages of the inflammatory process the causative organisms lie chiefly beneath the epithelial surfaces and, therefore, escape detection by routine cultural methods. In most outbreaks bacteriological findings have been so inconstant and so confusing that many investigators believe that the cause of colds has not yet been discovered, and that the rôle of the usual micro-organisms is chiefly that of secondary invaders which follow a primary infection of unknown etiology.

The view that colds are caused by ultramicroscopic organisms is based upon this assumption. Acute coryza is said to have been transmitted to normal individuals by the instillation into their nostrils of coryzal excretions which have been freed of all bacteria by a Berkefeld filter. This seems to suggest that the cause of colds is a filtrable virus. Further investigation, however, is necessary before this hypothesis can be accepted, for many workers have been unsuccessful in transmitting colds by this procedure.

Environmental factors, such as chilling of the body, sudden cooling after exercise, the wearing of wet shoes and clothing, fatigue, and irritants in the air, often precipitate the onset of a cold. Data collected in isolated communities indicate, however, that physical hardships of such character do not *per se* induce coryza unless an infecting agent is also present. Although the exact effect of chilling is not understood, experiments indicate that susceptibility to infection is increased when the body is subjected to sudden temperature changes. In man such changes also produce definite ischemia and localized cooling of the nasopharynx which apparently render this region especially vulnerable to bacterial action. When the local resistance is sufficiently disturbed ordinary organisms of the nose and throat may act as primary invaders and give rise to typical colds. The latter type of infection is especially common among individuals with structural or inflammatory abnormalities of the upper respiratory tract. Lesions such as hypertrophied adenoids, nasal polyps, chronic sinusitis, or chronic catarrh often harbor pathogenic bacteria and also disturb the mechanism by which drainage from the nose and throat normally takes place.

Epidemics of upper respiratory infection of considerable magnitude are sometimes caused by organisms such as the *Streptococcus* which seem to have a specific affinity for tissues of this region. Such virulent bacteria need no previous injury of the mucous membranes to enable them to invade the epithelium. At times unusual organisms have been found to be the cause of certain outbreaks, but usually the etiological agents consist of special strains of the common inhabitants of the nose and throat, and are differentiated from them with great difficulty. The factors which increase and decrease the virulence of these groups are not determined, but rapid transmission from one non-immune subject to another is probably of the greatest importance.

Thus it may be seen that the common cold may comprise a group of different affections: some may be caused by a filtrable virus; others by organisms with special virulence for the tissues of the nose or throat; while many are produced by factors which lower resistance and allow the common pathogens of the upper respiratory tract to invade the mucous membranes.

Morbid Anatomy.—The characteristic lesion of the common cold is a catarrhal inflammation of any part of the upper respiratory tract or paranasal sinuses. The process often begins at a focal area and spreads as the causative organisms and irritating bacterial substances are disseminated through the network of lymphatics beneath the epithelial surface. The local reaction frequently stimulates a vasodilatory reflex, which increases the engorgement of the spongy tissues of the nose.

The mucous membrane is red and thickened and is covered by an excess of seromucoid secretion that becomes purulent in the later stages. The lymph-glands which drain the infected area are often enlarged, and the small follicles in the walls of the pharynx stand out as tiny, glistening bodies. Microscopical examination shows nothing except hyperemia and edema of the tissues, and, in the later stages of the inflammatory process, an increase of wandering cells.

The systemic reactions that frequently accompany coryza result from absorption of bacterial products from the diseased area. Individuals differ in their response to these substances, and the type of organism usually determines the severity of symptoms.

Epidemiology.—Diseases of the upper respiratory tract are often highly contagious and may spread readily among the members of a household or a community. At times, however, the disease seems limited to a single individual and is not contracted even by those in close contact with the patient. Both epidemic and sporadic types are much more common during the colder months of the year. They are especially numerous in the autumn, late in September or during October; in midwinter, during January and February; and again in the spring, usually in April. This seasonal variation does not depend entirely upon weather conditions, as is popularly supposed, for the periodicity and severity of colds has been found strikingly similar in various regions irrespective of climatic differences. Perhaps the factor of greatest importance is the change to an indoor life during the winter months. In schools especially, students are closely associated in classrooms where various bacteria of the respiratory tract are readily disseminated throughout the group. Under conditions such as these the virulence of some of the organisms may be greatly enhanced as they are transferred rapidly from one non-immune subject to another. Infection, once established, is spread by sneezing, coughing, expectoration, and blowing the nose, all conspicuous features of colds.

Symptoms.—The onset of coryza is usually marked by sensations of burning or itching at the primary area of invasion. This is generally in the posterior nares, but may be in any portion of the upper respiratory tract. In about 30 per cent. of cases the inflammation remains localized, but in many instances the nose, pharynx, larynx, trachea, and paranasal sinuses become extensively involved.

At the height of the disease patients are quite dejected and uncomfortable. The conjunctivæ are suffused, the nasal mucosa is red and swollen, the nostrils are partly or completely occluded, and from them pours continuously a watery discharge, which causes much sniffling and blowing of the nose. Areas of excoriation appear at the nasal orifices and around the mouth. Headache and dull pain in the face and back of the nose are common and are aggravated by inspiration of air. The sense of smell, taste, and hearing is often impaired. The voice becomes husky and muffled; marked hoarseness indicates laryngeal involvement. The tongue is dry and coated. Swallowing and opening the mouth may be painful or difficult. Non-productive coughing is often the most distressing symptom; with trachitis, it is associated with a sensation of tightness and soreness behind the sternum. The lymph-nodes near the angle of the jaw and in the neck may be swollen and tender. Constitutional symptoms appear early, and vary extremely in severity even during a single epidemic. They are not in proportion to the extent or appearance of the lesion in the nasopharynx. In mild cases there is definite languor and disinclination for all exertion. With more severe infections prostration is striking. Usually there is a slight elevation of temperature (100°–102° F.). Patients complain of vague aching in the back and extremities. Their hands and feet are often cold, and they wear additional clothing to protect themselves from drafts, to which they are particularly sensitive. Other organs besides those of the respiratory tract may also be affected and produce symptoms, the commonest of which are constipation, diarrhea, anorexia, abdominal cramps, and nausea. Arthralgia, neuralgia, and areas of hyperesthesia are occasionally noticed, especially after the acute stages.

The symptoms may last a few days or many months. Bronchial involvement and pyogenic infections of the sinuses and middle ears run a tedious course. As recovery from the cold progresses congestion gradually diminishes and the secretions become scanty and more purulent. During convalescence there may be weakness, a loss of weight, nervousness, and insomnia.

Diagnosis.—Typical coryza offers but few diagnostic difficulties. Certain specific diseases, such as *measles, diphtheria, scarlet fever, pertussis,* and *typhoid fever,* may produce catarrhal symptoms at the onset, and are consequently mistaken for infections of the upper respiratory tract until more characteristic features develop.

Grippe and *influenza* are closely allied to the common cold. In these conditions the substances absorbed from the infected area in the respiratory tract are especially toxic. The differential diagnosis depends upon the relative severity of symptoms. In the same outbreak all gradations between grippe and a mild congestion of the nasopharynx can be observed.

A mild or aborted cold is easily confused with non-infectious hyperemia of the nasal mucous membranes due to such causes as local irritants, drugs, allergic reactions, and various vasomotor phenomena. Even with a careful history definite diagnosis may be impossible.

Prophylaxis.—Measures to prevent colds are of various types. The most effective, perhaps, is reducing to a minimum contact with crowds and infected individuals. Strict *isolation* is obviously impossible except for invalids and very young children.

Spraying and *gargling* with antiseptics are usually ineffectual because it is impossible to free the mucous membranes of bacteria by this method. *Irrigations* are of value only when abnormalities in the nose or throat impair the natural mechanisms of elimination. In such cases only the blandest solutions should be employed.

Vaccines are of limited value, for it is impossible to include in a stock preparation all the strains of organisms which produce catarrhal symptoms. Statistics confirm this by showing that subjects inoculated with stock vaccines contract colds about as readily as the uninoculated. For patients, however, who suffer from repeated reinfections because of a chronic focus in the respiratory tract, autogenous vaccine therapy is rational and often successful. Usually, infected foci should be removed surgically. Children especially have fewer colds after *tonsillectomy* or *adenoidectomy.*

Exposure to chilling and *out-of-door hardships* are sometimes recommended to increase the resistance to respiratory diseases. Fresh air minimizes the chance of infection, but probably does not affect the susceptibility of the individual. Colds are as common among robust athletes as among individuals leading sedentary lives. Experience usually shows that ample clothing, dry, warm shoes, and moderate exercise are better prophylactic measures than most "hardening" procedures.

Patients subject to frequent colds often find relief by seeking semitropical climates during the winter months.

Treatment.—*Local application of antiseptics* to the nose and throat is usually valueless in the treatment of colds, as it is difficult to destroy the causative organisms beneath the epithelial surfaces. Only in the earliest stages of infection should bactericidal drugs be recommended. Argyrol (20 per cent. solution) dropped into the conjunctival sacs and nostrils seems

to arrest the development of symptoms in some cases. Inhalation of chlorin gas (0.015 mgm. per liter of air for one hour) is a recent method of treating respiratory diseases. The preliminary reports regarding its merits are conflicting, but, on the whole, seem rather disappointing.

The treatment of colds consists mainly in the *relief of symptoms* as they arise. Patients are usually more comfortable in bed, although in most instances they prefer to continue their daily occupation. Rest should be made imperative if the temperature rises above 100° F., or if there is evidence of such formidable diseases as diabetes, nephritis, rheumatic fever, cardiac lesions, or pulmonary infections. *Isolation* is desirable, as it protects others and minimizes the opportunity of acquiring secondary infections during a phase of increased susceptibility. The body, especially the feet, should be kept warm and dry. Smoke, cold, damp air, and other irritants must not enter the respiratory tract. Ingestion of fluids in liberal amounts helps diminish the toxemia. Any simple diet is suitable. An occasional saline cathartic is indicated even when the bowels are active.

Striking relief from malaise and aching is afforded by some of the *coal-tar derivatives*. Phenacetin (gr. v, 0.3 gram) with soda bicarbonate (gr. xv, 1.0 gram) every three hours is a well-known combination. An excellent grippe capsule contains:

Codein sulphate	gr. $\frac{1}{4}$	015;
Acetylsalicylic acid	gr. v	3 ;
Phenacetin	gr. ij	12;
Caffein citrate	gr. ss	03.

If discomfort is marked, one of these may be given as often as every three hours.

Measures to promote sweating and vasodilatation also add to the comfort of the patient. Hot foot baths and warm drinks are often used to supplement analgesics such as Dover's powders (gr. x, 0.6 gm.) or whisky.

Local irritation in the nose or throat is best relieved by spraying at frequent intervals with one of the many *aromatic oil preparations*. One that is quite satisfactory contains:

Thymol	gr. $\frac{1}{4}$	015;
Menthol	gr. ij	12;
Eucalyptol	$\mathfrak{m}$ v	3.
Liquid albolene	$\mathfrak{z}$ j 30	

Some patients find relief in *nasal irrigations* of warm normal saline or 2 per cent. boric acid solution before using the oil. Fumes of menthol either from a patented inhaler or from impregnated wool placed in the nose diminish the feeling of "stuffiness" in the nostrils.

Ulceration of the mucous membranes or tonsils should be swabbed with mercurochrome (2 per cent. solution) or some other *antiseptic* several times daily.

Patients with laryngitis or tracheitis should rest the voice as much as possible. Violent coughing is also irritating, and should be controlled by codein in sufficient doses if the usual emulcent or expectorant cough mixtures prove ineffectual. Relief is also afforded by inhalations from a vessel containing about a pint of hot water and a teaspoonful of compound tincture of benzoin or oil of pine.

Tender glands in the neck are best treated by intermittent application of ice-bags.

Pain and tightness under the sternum is benefited by counterirritants such as turpentine liniment, mustard plasters, or flaxseed poultices.

The possibility of acute pyogenic complications, such as sinusitis or otitis media, must constantly be considered. Many of these subside spontaneously with conservative treatment; therefore operation in most cases should be deferred until the need for surgical drainage is imperative.

Rest with a vacation is important after a severe cold. It is unwise to permit patients to return to full activity in a weakened condition. Nourishing food, sunlight, and avoidance of fatigue are essential. Tonics, especially those containing nux vomica, are beneficial.

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INFLUENZA

Definition.—Influenza is a highly contagious, specific infectious disease which occurs most characteristically in epidemic and pandemic outbreaks, during which it spreads with extraordinary rapidity. The principal mani-

festations are sudden onset with fever, marked prostration, severe aching pains in the back and extremities, conjunctival injection, and a rapidly progressive inflammation of the respiratory mucous membrane. It is self-limited and of short duration. In itself it is rarely serious, but because of its great prevalence and especially because it predisposes to frequent and highly fatal secondary infection of the lungs it often leads to serious consequences.

History.—Although there is little doubt that influenza is a disease of great antiquity, its authentic history, according to Leichtenstern, begins with the European epidemic of 1510. Since that time numerous epidemics have been recognized and recorded in all parts of the world. At least eight great pandemics with their preceding and succeeding epidemics have occurred—1580, 1729–32, 1780–82, 1830–33, 1836–37, 1847–48, 1889–92, and 1918–20.

Epidemiology.—The history of influenza shows that great pandemics sweep the world at irregular intervals. Each pandemic typically exhibits *three major epidemic periods or waves*, separated from each other by a distinct interval of time. These succeeding waves are clearly recognizable in the pandemics of 1889–92 and 1918–20. The *first wave*, though it affects great numbers of persons, is relatively mild and is not attended by a high incidence of complications. For this reason it is frequently not recognized as influenza, and is hailed as a new disease by each generation ignorant of the classical picture of the disease in its epidemic form. The *second wave* also attacks great numbers of persons, but is more severe than the first, and is accompanied by a high incidence of complications, especially pneumonia, with a resultant excessive mortality. During the *third wave* the number of persons attacked is somewhat less, but complications are frequent and severe.

Three major theories concerning the *source of these great pandemics* exist. The first, put forward by Leichtenstern and others, suggests that they arise from one or more endemic foci in the East and spread westward, encircling the globe. The second assumes that influenza is endemic throughout the major part of the world, and that the great pandemics may arise from any one of a number of foci or even perhaps more or less simultaneously from two or three. The third also assumes that influenza is universally endemic, but that pandemics originate in a simultaneous enhancement of the virulence of the influenza virus wherever the disease exists in endemic form. Although the first of these theories had been generally accepted before the pandemic of 1918–20, much evidence was accumulated during and after the pandemic which indicates that the second theory is probably more nearly correct (Zinsser, Vaughan, Frost).

In addition to the recurrent cyclical nature of pandemic influenza, the most *characteristic epidemiologic features* are the extraordinary rapidity of spread, the very high attack rate, the relatively short duration of the individual waves, and the occurrence of more or less localized epidemics of decreasing severity in the years following a pandemic. The rapidity of the spread of influenza is due to the combination of a fairly general susceptibility and the relatively short incubation period (about forty-eight hours). It is determined in any given area by the rapidity of the existing means of travel and the extent of human intercourse, being most rapid in thickly settled communities, less so in sparsely populated districts.

The *morbidity* from influenza during pandemic periods is very high, the best statistical studies placing it between 200 and 400 per 1000. While people of all ages are susceptible, the *highest incidence* is between the *ages* of five and forty. Females appear to be slightly more susceptible than males, but the difference is inconspicuous and perhaps determined by factors other than sex.

The *duration of a primary epidemic wave* in a single community varies somewhat in different localities, but is always relatively short—three to six weeks. Although every primary epidemic undoubtedly has a preliminary invasion period of two weeks or more during which the number of cases gradually increases, this is frequently overlooked, so that an epidemic appears to develop with extraordinary rapidity, reaching its peak within one to two weeks at the most. Within another week or two the incidence falls to nearly normal. The explosive nature of the outbreaks, which is more characteristic of influenza than of any other disease, may be explained by the short incubation period; by the susceptibility of large masses of people; by the fact that many who are attacked continue to work and thus spread the disease, and by the ease with which primary respiratory infections are transmitted. The *secondary wave* presents the same general features, but the period of decline is somewhat less rapid and is frequently interrupted by a period of recrudescence. The *tertiary wave* develops more slowly, the peak is not sharp, and the period of decline is less rapid, the epidemic lasting for between eight and ten weeks. This alteration in the form of the successive waves is probably due to a partial residual immunity of those attacked in the first and second waves.

Intimately related to the periodic development of influenza pandemics is the question of endemic influenza and of localized epidemics which occur at frequent intervals in one or another part of the world during interpandemic periods. Lack of precise knowledge of the bacterial etiology of influenza and the difficulties of differentiating surely the ordinary common colds, the more severe catarrhal fever (commonly called *grippe*), and true influenza, if these be distinct etiological entities, make it impossible to answer this question at the present time. The writer thinks it most probable that true influenza in mild form is widely endemic, that small local epidemics of somewhat greater severity are of relatively frequent occurrence, but that only in the presence of pandemics when the disease occurs with an exaggerated severity is it certainly recognizable as true influenza.

Etiology.—The epidemiological and clinical features of epidemic influenza indicate that it is caused by an easily transmissible virus possessing a high degree of primary pathogenicity. The occurrence of fulminating epidemics and pandemics, together with the relatively transient immunity following an attack, suggests that the virus is subject to rapid alterations in virulence. While these factors probably play an important rôle in determining the development of epidemics, there are doubtless many others of even greater importance which are not understood at the present time. There is much uncertainty concerning not only the cause of epidemic outbreaks but also the specific bacterial cause of the disease. Two important theories hold sway at present: (1) Influenza is caused by *Bacillus influenzæ*, originally described by Pfeiffer in 1892. This theory was generally accepted until the pandemic of 1918, but has since been seriously questioned. (2) Influenza is caused by a filtrable virus, *Bacillus influenzæ* being merely

a secondary invader. The only filtrable organism at present deserving consideration is *Bacterium pneumosintes*, discovered by Olitsky and Gates.

Bacillus influenzæ is a small Gram-negative, non-motile, hemophilic bacillus, isolated with difficulty unless great attention is paid to its fastidious growth requirements. During an attack of influenza it is found in immense numbers on the mucous membranes of the respiratory tract, but it rarely penetrates deeply into the tissues and even more rarely invades the bloodstream. It has an extraordinarily labile virulence for animals, but under proper conditions has been shown to possess a marked pathogenicity for mice, guinea-pigs, rabbits, and monkeys.

The arguments in favor of considering *Bacillus influenzæ* to be the cause of influenza are: (*a*) The very frequent isolation of the bacilli from the respiratory mucous membrane, frequently in immense numbers and in almost pure culture, in early uncomplicated cases (90 to 100 per cent.); (*b*) its predominant presence during the acute stage of the disease when there is rapid recovery without development of complications; (*c*) its occasional presence *in pure culture* in the lungs when influenza has been rapidly fatal; (*d*) its very occasional isolation in pure culture from the blood within a short interval after the onset of the disease; (*e*) its almost constant presence in all varieties of early and late complications; (*f*) the peculiar distribution of the bacilli in the large and small bronchi in fatal cases; (*g*) the rapidly increasing prevalence of these organisms in normal individuals as an epidemic progresses, which indicates that actual dissemination readily occurs and is very widespread during pandemic periods; (*h*) their diminishing occurrence in normal and diseased respiratory passages as epidemics decline; (*i*) certain characteristics of the organism—the tendency to grow on the respiratory mucous membrane, the production of potent poison (Parker), and the lability of virulence—harmonize with the entire clinical complex of epidemic influenza; (*j*) the fact that inoculation of the nasal and pharyngeal mucous membrane of monkeys with *Bacillus influenzæ* has shown that it is a primary pathogen capable of inducing a disease essentially identical with influenza in its clinical course, symptoms, complications, and pathology (Blake and Cecil). The arguments against the etiological importance of *Bacillus influenzæ* are: (*a*) The frequent failure of some bacteriologists to find the organism in early cases; (*b*) the presence of the bacilli in normal individuals and as secondary invaders in measles, whooping-cough, etc.; and (*c*) the apparent antigenic multiplicity of strains isolated during epidemics. None of the evidence *pro* or *con* is entirely conclusive (Holman, Opie *et al.*, Zinsser).

Satisfactory evidence that influenza is caused by a *filtrable virus* is meager, the only observations deserving serious consideration being those of Olitsky and Gates. They have isolated from the nasopharyngeal secretions of a limited number of cases during the first thirty-six hours of the disease a minute, filtrable, bacillary organism to which they have given the name *Bacterium pneumosintes*. It was recovered from patients with typical influenza in the 1918–19, 1920, and 1921–22 epidemics, but not from other sources. It is moderately pathogenic for rabbits, inducing a hemorrhagic lesion of the lungs accompanied by mild conjunctivitis, febrile reaction, and a leukopenia, especially of the lymphocytes. It increases the susceptibility of these animals to secondary infections. The strains so far isolated are immunologically homologous. Its etiological relationship to influenza is at

present uncertain, but the data presented are sufficiently suggestive to warrant further investigation of this organism.

Bacteriology.—Whatever the primary cause of influenza, the organism most consistently found in the secretions of the respiratory tract during life, both in the simple and the complicated cases, is *Bacillus influenzæ*. At autopsy in fatal cases it is usually present in the pus from infected sinuses and in the exudate throughout the bronchial tree down to the terminal bronchioles. It is much less frequently found in the lung tissue and only rarely invades the pleural or pericardial cavities. It very rarely enters the blood-stream or localizes in other organs of the body. A great variety of other bacteria are found as secondary invaders in complicated cases. The most important are the *Pneumococcus*, of which Type IV is the most common, *Streptococcus hemolyticus*, and *Staphylococcus aureus*. Other organisms less frequently found are non-hemolytic streptococci, *Staphylococcus albus*, *Micrococcus catarrhalis*, *Friedländer's bacillus*, and *Meningococcus*.

Morbid Anatomy.—So far as is known, simple uncomplicated influenza causes no characteristic changes which serve to differentiate it from other catarrhal inflammations of the respiratory mucous membrane. In severe, rapidly fatal cases of influenza with pneumonia, when no bacteria except *Bacillus influenzæ* can be found in the bronchi and lungs, there is, in addition to the rhinitis and pharyngitis, an intense tracheitis and bronchitis, often hemorrhagic, a very marked bronchiolitis with epithelial necrosis and serosanguineous exudate in the lumen, peribronchiolar and hemorrhagic pneumonia, marked alveolar edema and emphysema with a characteristic hyaline fibrin lining the distended air spaces, and little or no pleural involvement. In later cases in which secondary infection with other bacteria has occurred, the pathology of the lungs is complex. The noteworthy characters referable to the severity of the primary injury in the lower air passages are acute bronchitis with injury or destruction of the lining epithelium; purulent bronchiolitis; peribronchiolar pneumonia, often hemorrhagic; susceptibility of the bronchi, bronchioles, and pulmonary tissue to secondary pyogenic infection with necrosis and suppuration; bronchiectasis, and a marked tendency to chronic pneumonitis due to organization (Klotz, Opie *et al.*, Winternitz *et al.*, Wolbach).

The *paranasal sinuses* frequently show intense inflammation of their mucous membranes and contain purulent exudate. Hemorrhages may occur in the *skeletal muscles*, especially in the rectus abdominis, also in the pericardium, spleen, kidneys, adrenals, testes, and cerebrum. *Subcutaneous emphysema* chiefly about the neck and thorax is sometimes found. Other lesions found in fatal cases are attributable to secondary infection and are given below under Complications.

Symptoms.—The *incubation period* lasts from one to three days, usually about forty to forty-eight hours. The *onset* is sudden, with fever, chilly sensations, and prostration accompanied by catarrhal symptoms referable either to the nose, the pharynx, or the trachea. Depending upon the severity of the infection, the subsequent course of the disease is so variable that it can best be described by division into types.

Simple Form Without Complications.—Simple uncomplicated influenza comprises more than 95 per cent. of the cases during the first wave of a pandemic, 70 to 90 per cent. in the subsequent waves. The *onset* is usually sudden without a period of invasion. The initial symptoms are

chilliness, extreme general malaise, and severe aching pains throughout the whole body, but especially in the back and extremities. A varying degree of prostration, sometimes leading to complete collapse, is almost invariably present. Severe headache is common. Stupor or delirium occasionally occurs. The temperature rises rapidly, ranges from 100° to 106° F., in most cases being between 102° and 105° F. The pulse rate varies between 80 and 100, and the respiration rate is slightly accelerated. The patient appears listless, the face and often the neck and upper thorax are deeply flushed, the conjunctivæ are injected, the pharyngeal mucosa is intensely congested. Shortly after onset coryza begins, or sore throat due to the pharyngitis, or soreness behind the *manubrium sterni*, with a dry irritative cough due to tracheitis. Epistaxis is fairly frequent, occurring in 10 to 15 per cent. of the cases. Gastro-intestinal symptoms are insignificant, nausea, vomiting, and diarrhea being rare.

The *subsequent course* of the disease is brief. The fever persists for from one to five days, in the majority of cases from two to four days. The respiratory symptoms become more marked, usually being well developed at the end of twenty-four hours. They may remain localized in the nose, the pharynx, or the trachea, but more commonly spread rapidly throughout the respiratory tract, sometimes as far down as the larger bronchi. The progress of respiratory infection is marked subjectively by sensations of irritation, stinging, and a feeling of tightness. A thin, mucoid exudate appears, which later may become mucopurulent. With the development of tracheitis there is a sense of burning and tightness beneath the sternum, accompanied by a harassing cough. The sputum, which at first is scanty, mucoid, and sometimes streaked with blood, later becomes mucopurulent. Laryngitis occasionally develops. Examination of the chest reveals little abnormality except when involvement of the larger bronchi gives rise to scattered rhonchi and sibilant râles.

Examination of the *blood* shows a leukopenia in most cases during the acute stage, although in the mildest cases the white count may be normal or even slightly elevated. Opinion differs as to whether the leukopenia is due to depression of the polymorphonuclear leukocytes or the lymphocytes, the majority of authors favoring the former view. Blood-cultures are sterile except when in rare cases *Bacillus influenzæ* is present. The *urine* frequently shows a febrile albuminuria.

Recovery is prompt, the temperature usually falling by rapid lysis, occasionally by crisis. Although convalescence is rapid in most of the simple cases, it may be attended by a prolonged period of depression and asthenia. *Relapses* do not occur and there are no fatalities in this type of the disease.

Simple Form With Complications.—Between the simple uncomplicated form of influenza and the severe pneumonic form there is a type which is prolonged by the development of a purulent bronchitis. This begins insidiously without any prominent symptoms to mark its onset. About the third or fourth day of influenza, when recovery from the primary disease is expected, the patient begins to cough more frequently, and to raise increasing amounts of mucopurulent sputum which eventually becomes frankly purulent. This may be quite abundant and is often somewhat nummular in character. It practically always shows the presence of *Bacillus influenzæ* together with one or more other organisms, such as *Pneumococcus*, *Streptococcus*, or *Micrococcus catarrhalis*, when cultured. Examination of the

chest reveals numerous coarse, medium, and fine moist râles more or less diffusely scattered throughout the lungs, usually most numerous over the lower lobes. The percussion note, breath and voice sounds, and vocal and tactile *fremitus* remain normal. A moderate elevation of temperature, rarely above 101° F. and of irregular character, usually persists for a few days or a week. There is little or no increase in the respiration or pulse rates, and cyanosis is unusual in the absence of bronchopneumonia. In many cases a persistent cough due to chronic bronchitis continues for weeks. Sometimes a mild degree of chronic bronchiectasis results. Another complication which not infrequently accompanies the simple form of influenza is a mucopurulent sinusitis affecting any or all of the paranasal sinuses. Otitis media also occurs, more commonly in children.

This form of the disease comprises 10 to 15 per cent. of the cases in the second and third pandemic waves and is not infrequently encountered in interpandemic periods, especially in the localized epidemics that occur preceding and following pandemic outbreaks.

Pneumonic Form.—During the second and third pandemic waves from 5 to 15 per cent. of all patients develop pneumonia. In a large majority of instances the pneumonia is caused by a mixed infection of the bronchi and lungs with *Bacillus influenzæ* and one or more associated organisms, the most common being *Pneumococcus, Streptococcus hemolyticus*, and *Staphylococcus aureus*. Of the pneumococcus infections 85 to 90 per cent. are caused by the ordinary mouth pneumococci, Type II (atypical), Type III, and Type IV. In some cases *Bacillus influenzæ* alone is found. In a few instances of fulminating, rapidly fatal infection no organisms have been found. The pathology and to some extent the clinical course of the pneumonia is determined by the bacteria concerned (Opie *et al.*). It is clear that pneumonia in general should be regarded as a complication of primary influenza, even though a limited number of cases may occur in which the disease is pneumonic from the outset and fatal before secondary organisms invade the lungs.

Clinically, the pneumonic form may be divided into three types, which, it is true, overlap in any large series of cases. These are: (1) A fulminating rapidly fatal form in which pneumonia is present from the outset; (2) a progressive form in which on the second to fourth day the signs of pneumonia begin to develop without the appearance of any decline in the fever; (3) a late form in which, after apparent recovery from the primary influenza, pneumonia suddenly supervenes on the fourth to tenth day after onset.

In the first form, which is comparatively rare and ordinarily occurs only during the rise and height of the second pandemic wave, the onset, in addition to the symptoms of simple influenza, is accompanied by great respiratory distress, intense cyanosis, and signs of rapidly developing hemorrhagic edema of the lungs. The condition is very alarming. Patients thus affected may die within twenty-four to forty-eight hours.

The second and third forms differ only in time of onset of the pneumonia and may be discussed together. The primary influenza is the same as in the simple form. The onset, symptoms, physical signs, and course of the pneumonia are very variable, ranging all the way from those of a mild bronchopneumonia with limited pulmonary involvement, from which there is prompt recovery in four or five days with defervescence by lysis or crisis, to those of a rapidly progressive, coalescing pneumonia with fatal outcome. In some

cases the picture is that of lobar pneumonia, in others there is a long-drawn-out course due to necrotizing or organizing processes. Certain features deserve special consideration. In many cases the areas of pneumonia are isolated and deep seated, so that, in spite of the severity of the condition, the typical signs of consolidation do not appear until comparatively late. The involvement is nearly always bilateral. The signs usually appear first over the lower lobes and are apt to vary greatly from day to day as the disease progresses. The temperature curve is very irregular. The pulse, except during the last thirty-six hours in fatal cases, is apt to be slow in proportion to the temperature. The respiratory rate varies with the severity of the disease. Cyanosis, which is a prominent feature, is largely of the lilac or heliotrope type, and indicates insufficient oxygenation of the blood as it passes through the lungs. Early pleurisy, except in hemolytic streptococcus infections and in the rapidly coalescent cases, is uncommon. The character of the sputum varies. It may be scanty, bloody, and mucoid or profuse, purulent, salmon pink, or yellowish green, the latter type being associated with an extensive bronchiolitis or bronchiectasis. The leukopenia of the primary influenza frequently continues throughout the course of the pneumonia, especially in the severe cases. A relative polycythemia often occurs when the disease is rapid and severe, the red blood-cell count sometimes reaching 8,000,000 per cubic millimeter. Blood-cultures are rarely positive except at the end of the infection, the serious features of the disease probably being due to toxemia and anoxemia rather than to septicemia. Recovery is frequently delayed by the formation of abscesses and by failure of resolution. Sudden death occasionally takes place during apparent recovery. Convalescence is often prolonged. Chronic bronchitis and bronchiectasis are frequent sequelæ.

Complications.—Influenza predisposes to secondary infection with a variety of organisms. Whether this is preponderantly due to lowering of general resistance by the extreme prostration of the disease and the inhibition of leukocytic defense, or to a destruction of local resistance against bacterial invasion by profound injury to the respiratory mucosa, or to a combination of both factors, is uncertain. It seems most probable that both are concerned. At any rate, complications are numerous and varied, and in large part determine the mortality of the second and third pandemic waves. The most frequent and important complications are acute sinusitis, otitis media, with or without acute suppurative mastoiditis, purulent bronchitis and bronchiolitis, bronchiectasis, and pneumonia. The pneumonia itself may be complicated by the development of pulmonary abscesses, especially when *Streptococcus hemolyticus* or *Staphylococcus aureus* are present. Empyema is common in the streptococcus cases and usually begins relatively early in the course of the pneumonia. Mediastinitis, pneumothorax, and subcutaneous emphysema may occur.

Erythema, simple purpura, and subcutaneous abscesses occasionally appear. Herpes is infrequent. Rupture of the rectus abdominis muscle, with hematoma, has been noted in a considerable number of cases. Epistaxis is frequent, hemoptysis and hemorrhage from the bowel much less so. The circulatory system is not commonly affected, but pericarditis, endocarditis, and thrombophlebitis are occasional complications. A postinfluenzal bradycardia sometimes develops. Tympanites is frequent in the toxic pneumonic cases and a moderate icterus may develop. Peritonitis is a rare

complication. Arthritis and osteomyelitis have been observed with influenza. Nephritis is rare. Meningitis, hemorrhagic encephalitis, and multiple neuritis occasionally occur. Transient postinfluenzal psychoses are seen.

The *commonest sequelæ* are chronic bronchitis, chronic bronchiectasis, and pulmonary fibrosis. These conditions may persist throughout life and not infrequently lead to a mistaken diagnosis of pulmonary tuberculosis. They frequently make their victim susceptible to repeated attacks of acute bronchitis and pneumonia.

Diagnosis.—There is no single pathognomonic feature upon which a diagnosis of influenza may be made. During pandemics, however, the diagnosis is not difficult in the majority of cases. The sudden onset of a febrile attack with severe prostration and aching pains in the back and legs, which are out of proportion to the catarrhal symptoms, together with the flushed face, injected conjunctivæ, intensively congested pharynx, and a leukopenia are the characteristic manifestations. The presence of *Bacillus influenzæ* in large numbers in the secretions of the respiratory tract is suggestive, but no bacterial test can be considered final until the cause of influenza is definitely established. When there are numerous other cases the foregoing features warrant a diagnosis of influenza. During interpandemic periods the diagnosis is always more or less doubtful, since there is no definite means of distinguishing between a severe common cold and relatively mild influenza. The recognition of complications depends upon the characteristic symptoms and physical signs of the condition in question. Whenever the fever persists for more than four days a complication should be suspected and carefully looked for.

Prognosis.—The prognosis of simple uncomplicated influenza is excellent. This type of infection does not cause death. In simple cases with the less serious complications, such as sinusitis, laryngitis, and bronchitis, the prognosis is also good and recovery takes place unless further complications develop. Purulent bronchiolitis and bronchiectasis, however, may result in chronic pulmonary disease which persists for years with periods of exacerbation and remission. With the onset of pneumonia the prognosis becomes serious, the mortality rate varying all the way from 15 to 60 per cent. under varying circumstances. The degree of cyanosis and the respiration rate are probably the two most important prognostic signs. A persistent and progressively increasing cyanosis, particularly of the heliotrope type, and a progressively rising respiration rate nearly always indicate a fatal outcome. Even when patients appear to be doing well a sudden change for the worse may supervene at any time, so that prognosis should be cautious until convalescence is well established. In pregnancy the prognosis is always serious, the mortality high.

Prophylaxis.—There is no specific prophylaxis for influenza. The only preventive measure of proved value is absolutely complete isolation, which is a practical impossibility except under very exceptional circumstances. Individuals should, however, avoid crowds and contact with known cases during a pandemic wave. Although little can be done to prevent the spread of influenza, much can be done to lessen the incidence of complications by the proper treatment of patients. The prophylaxis of the complications is the treatment of the disease.

Treatment.—There is no specific cure for influenza. The most important

forms of treatment are: (1) Absolute confinement to bed *from the onset of the disease until convalescence is well established* and the danger of complications is past; (2) administration of large quantities of fluid (3500 to 5000 c.c. daily) during the febrile period; (3) isolation from sources of secondary infection and the practice of medical asepsis by those coming in contact with the patient. If these are rigidly adhered to the incidence of complications may be greatly reduced. During the acute period the diet should be light. For the headache an ice-cap should be employed, and if necessary phenacetin (0.3 gm.) or pyramidon (0.3 to 0.6 gm.) should be given. Aspirin (0.6 gm.) may be used for the general aches and pains. If there is sleeplessness, Dover's powder (0.6 gm.) may be used. A simple enema should be given to relieve constipation. The use of an inhaling mask is of value in allaying the irritation of the respiratory mucous membranes. Five to 10 drops of the following mixture should be placed on the sponge at intervals as necessary: menthol, 1 part; creosote, 1 part; chloroform, 1 part.

The treatment of the complications does not differ from their treatment when they occur alone and is outlined in the appropriate chapters.

Francis G. Blake.

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LOBAR PNEUMONIA

(Croupous or Fibrinous Pneumonia)

Definition.—An acute infectious disease, caused usually by the pneumococcus, and characterized by a massive inflammatory exudate in one or more lobes of the lungs. The dominant clinical features are chill, fever, pain in the side, and cough, with expectoration of rusty sputum.

History.—Pneumonia was well recognized by Hippocrates and other Greek students of medicine. Our clinical knowledge of the disease comes largely from Laennec, whose classical descriptions of the pathological changes and physical signs are surprisingly accurate, considering that they were written in 1819.

The etiology of pneumonia was unknown until 1881, when Pasteur and Sternberg independently noted the occurrence of small diplococci in the sputum of patients with lobar pneumonia. In 1884 Fraenkel definitely proved that the pneumococcus was the exciting agent of pneumonia, and further studies by Weichselbaum corroborated the work of Fraenkel.

Incidence and Distribution.—Pneumonia is one of the most serious infectious diseases that man is heir to. It is widely prevalent in the United States, Great Britain, and other civilized countries. It is very difficult to arrive at any accurate idea of the incidence of the disease, but the figures on mortality rates can be looked upon as reliable. In the registration area of the United States there were 112,821 deaths from pneumonia in 1917, a rate of 150.5 per 100,000 of population. Of these, 65,438 were due to lobar pneumonia; 37,947 to bronchopneumonia, and 9436 were unclassified. The accompanying table was prepared for the writer by Dr. L. I. Dublin, Statistician for the Metropolitan Life Insurance Company. This table shows the death rate per 100,000 for all forms of pneumonia: (1) among policy holders of the Metropolitan Life Insurance Company; (2) in the registration area of the United States. These figures indicate that during the decade extending from 1911 to 1920 the death rate for pneumonia remained fairly constant, excepting 1918, the year of the influenza epidemic, when it was approximately doubled. Since 1920 there has been a considerable drop in the death rate. Whether this drop is temporary or whether the rate will return again to the previous figure remains to be seen.

DEATH RATES PER 100,000 FOR PNEUMONIA—ALL FORMS

Metropolitan Life Insurance Company, Industrial Department and United States Registration Area, 1911 to 1924

Year.	Metropolitan Life Insurance Co. (Ages One and Over).					United States Registration Area (All Ages, Including Under One).		
	Total.	White.		Colored.		Total.	White.	Colored.
		Males.	Females.	Males.	Females.			
1924	72.3*	63.9*		133.1*		†	†	†
1923	77.6	74.8	65.1	161.0	119.5	109.0	†	†
1922	73.7	73.1	63.6	130.3	107.6	102.1	98.0	141.7
1921	67.8	66.7	59.8	121.4	90.7	88.3	84.5	128.0
1920	106.1	101.8	95.0	173.7	160.0	137.3	131.3	201.3
1919	117.2	115.9	103.5	196.7	163.8	123.5	118.6	175.4
1918	269.8	297.2	227.3	412.3	300.9	286.2	275.3	418.9
1917	121.0	128.8	96.6	244.9	152.5	150.5	142.6	249.6
1916	114.3	120.4	96.1	200.3	141.9	137.8	132.9	204.7
1915	106.5	107.7	92.6	176.8	142.1	133.1	127.8	229.0
1914	100.3	104.8	86.8	158.3	120.0	127.3	122.4	218.0
1913	106.1	112.8	89.2	184.5	118.3	132.6	128.0	216.2
1912	103.9	106.9	90.4	166.3	124.9	132.4	127.6	239.1
1911	115.3	120.7	98.0	188.2	137.7	133.9	128.7	249.5

* Provisional figures. Not yet available by sex.
† Not yet available.

Pneumonia is particularly prevalent in cities. It is a disease of the temperate zone, though it may occur in the tropics. A cold, damp, changeable climate predisposes to the disease. When it occurs in a warm climate, such as that of Panama, it is doubtless referable to sudden changes of temperature.

Pneumonia is a disease of the late winter and early spring. In New York City January, February, and March are the months during which the disease is most prevalent. In a series of 1082 cases observed at Bellevue Hospital over a period of two years, about 75 per cent. were admitted during these three months. July, August, and September showed the lowest incidence.

Etiology.—*The Exciting Cause.*—Lobar pneumonia is due in a large majority of instances to the pneumococcus. Other bacteria may occasionally act as the exciting cause, but such are exceptional.

The pneumococcus is a minute, lance-shaped, Gram-positive coccus, which grows usually in pairs, but sometimes, especially on artificial media, in the form of chains. It possesses a capsule which can be demonstrated in both body fluids and cultures. The pneumococcus grows best on media containing blood or serum. On blood-agar plates it produces a flat grayish colony surrounded by a light green zone. In plain broth or in blood broth the pneumococcus grows diffusely throughout the medium. The pneumococcus is distinguished from *Streptococcus viridans* by its solubility in bile and its ability to coagulate inulin. The pneumococcus is extremely virulent for mice, rats, rabbits, and monkeys. On the other hand, chickens and pigeons have a very high immunity against the germ. The pneumococcus does not produce a toxin in the ordinary sense of the word. When it is grown in media containing hemoglobin the latter is changed into methemoglobin.

Perhaps the most important of recent contributions to our knowledge of pneumonia is that of Dochez and Gillespie, who showed that pneumococci could be divided into four "types," based upon well-defined immunological differences. In a series of 720 cases of lobar pneumonia studied at the Rockefeller Hospital, pneumococcus Type I infections were the most frequent, comprising 34 per cent. of all the cases. About 33 per cent. fell into the Type II group and 10.8 per cent. in the Type III group; 22 per cent. were Type IV infections.

In a series of 1082 cases of lobar pneumonia studied by the writer in the wards of Bellevue Hospital 993 cases received careful bacteriological study; 911 of these, or 91.8 per cent., showed pneumococci in the sputum or other body fluids. *Streptococcus hemolyticus* was found in 53 cases and *Streptococcus viridans* in 21 cases, and there was 1 case in which the *Bacillus influenzæ* was isolated in pure culture. Four cases were caused by the *Friedländer bacillus.* In 1 case *Staphylococcus aureus* appeared to be the exciting cause.

In 911 cases of pneumococcus pneumonia in Bellevue Hospital the various types of pneumococcus were represented as follows:

Type.	Number of cases.	Incidence per cent.
Pneumococcus Type I	346	38.0
Type II	165	18.1
Type III	137	15.0
Type IV	263	28 9

The incidence rates for the various types admitted to Bellevue Hospital differ somewhat from the Rockefeller Hospital figures. If the Rockefeller Hospital series and the Bellevue Hospital series are combined we have the following:

Type.	Number of cases.	Incidence per cent.
Pneumococcus Type I	592	36.5
Type II	402	24.6
Type III	215	13.2
Type IV	422	25.9

The incidence of the types varies considerably from year to year. During epidemics of influenza there is usually a marked increase in the incidence of pneumococcus Type IV infections.

Epidemiology.—Generally speaking, lobar pneumonia is an endemic disease; it may take on epidemic form, however, under certain circumstances. It has long been known that many healthy individuals are pneumococcus carriers and, reasoning from this, it was formerly assumed that most cases of lobar pneumonia were autogenous infections. During the past few years, however, important studies on the epidemiology of pneumonia have been carried out at the Hospital of the Rockefeller Institute. In these studies cultures were made from a large number of healthy mouths in order to determine the relative incidence of the various types of pneumococcus.

In a study of 297 individuals the relative incidence of the four types was as follows:

Type.	Cases showing pneumococci.	Incidence per cent.
Pneumococcus Type I	1	0.8
Type II	0	0.0
Type II, atypical	22	18.9
Type III	34	28.1
Type IV	64	52.9
Cases showing no pneumococci	178	
Total	299	

From these figures it is clear that pneumococcus Type I and Type II are practically never discovered in the buccal secretions of healthy individuals. On the other hand, pneumococcus Type II, atypical, Type III, and Type IV are frequently found in the healthy throat.

When it is recalled that pneumococcus Type I and Type II cause approximately 60 per cent. of all lobar pneumonia, it is fair to conclude that pneumonia due to these types is not an autogenous infection, but follows invasion by these organisms from without. On the other hand, it is probable that a considerable proportion of the pneumonia caused by pneumococcus Type III and Type IV are traceable to organisms which the patient has been carrying for some time in his own mouth.

During convalescence it is only in exceptional cases that the same type of pneumococcus with which the individual is afflicted during the disease persists in the mouth for any considerable time after recovery. Usually the infecting organism disappears in from three to four weeks after the illness. After it disappears, either no pneumococci are present at all, or the infecting type has been replaced by one of the types usually found in the normal throat. These observations afford still further evidence that infection in pneumonia, particularly in Type I and Type II cases, occurs from without.

Pneumococcus Carriers.—Carriers of virulent pneumococci probably play an important part in the dissemination of the disease. The Rockefeller Institute workers showed that a considerable percentage of persons inti-

mately associated with patients suffering from pneumonia harbor in their mouths pneumococci of the same type as those in the patients. Whereas pneumococcus Type I and Type II are almost never found in normal saliva, it was shown that in a large series of healthy individuals who had come in contact with cases of lobar pneumonia, 13 per cent. were pneumococcus Type I carriers, and 12 per cent. pneumococcus Type II carriers. It was also shown that the pneumococcus is more frequently present in the throats of persons who have had pneumonia than in those of individuals never attacked by the disease; and that the type of pneumococcus found in the throat corresponds to the type of pneumococcus previously isolated from the patient.

Factors Predisposing to Pneumonia.—*Age.*—The most marked susceptibility to pneumonia occurs at the beginning and toward the end of life. Young children are more susceptible than older ones. The susceptibility increases gradually during adult life, becoming greatest in old age. The United States Census report shows, however, that 51.2 per cent. of all deaths from pneumonia occur between the ages of twenty and sixty-five, indicating that pneumonia also takes a heavy toll of human life during the years of greatest activity. The economic significance of this fact should not be overlooked.

It is interesting to note the relation of age to the incidence of pneumococcus types. In the Bellevue Hospital series Type I infections were by far the commonest type encountered in young people, comprising 50.7 per cent. of all cases that occurred between the ages of ten and twenty years, 44 per cent. of all cases between the ages of twenty and thirty years, and 42.5 per cent. of all cases between the ages of thirty and forty years. During the later decades Type I infections become progressively less common, constituting only 20.6 per cent. of the cases over sixty years of age.

In a series of 329 Type I pneumonias studied in Bellevue Hospital, 88.7 per cent. occurred in patients under fifty; only 11.2 per cent. occurred in patients over fifty. On the other hand, Type III infections are rare in the young, but common in middle-aged and elderly people. In patients under thirty years, less than 7 per cent. showed Type III infections; while in patients over sixty, 41.2 per cent. were referable to pneumococcus Type III.

In contrast to these variations in the incidence of pneumococcus Type I and Type III infections, the incidence of Type II and Type IV pneumonia was very little affected by age.

Sex.—Men are more frequently affected than women, probably because they are more exposed to the weather. The incidence of Type I and Type II pneumonia is distinctly higher in males than in females, while women appear to be particularly susceptible to Type III pneumonia. In the Bellevue Hospital series the incidence of Type III pneumonia was three times as great for women as for men. The incidence of Type IV pneumonia is also higher in women than in men. This difference in type incidence for the sexes can probably be explained by the fact that men are more exposed to the virulent types than women; the latter, when they do contract pneumonia, are more frequently infected with the types found in the healthy mouth.

Race.—Negroes are distinctly more susceptible to pneumonia than the white races. This was well demonstrated during the World War when the negro troops suffered much more than the whites from pneumococcus infections.

Occupation and Mode of Life.—Pneumonia, like tuberculosis, is most common among the poor and badly nourished. Individuals who are exposed to hardships and inclement weather are particularly liable to the disease. In the Bellevue Hospital series day laborers and sailors were the two largest groups of wage earners represented. Pneumonia is more common in the cities than in the rural districts. This is probably due, however, not so much to the actual living in the cities as to the existence of slum conditions in the centers of large population.

Personal Condition.—Fatigue is one of the most important predisposing factors, especially when chilling of the body takes place after profuse perspiration. Hunger is another important factor. Debility and emaciation render individuals more susceptible to the pneumococcus. In our large cities alcoholism is responsible for a great many cases.

Weather.—Sudden drops in the temperature predispose to pneumonia—exposure to cold of any kind is undoubtedly an important factor. As previously pointed out, the combination of cold and dampness, such as occurs in the early spring, affords the conditions most favorable to contracting the disease.

Previous Attacks.—Pneumonia shows a very definite tendency to recur in some individuals. The patient's immunity against the pneumococcus is high immediately after the attack, but apparently it does not persist for more than a year.

Morbid Anatomy.—The face and lips are livid, and bloody fluid may ooze from the nose and mouth. The striking pathological feature of pneumonia is the consolidation of the pulmonary tissue. This may be limited to one lobe, but usually, in fatal cases, two or more lobes are affected. According to most statistical studies the right side is more frequently involved than the left. In the series of cases studied by the author, the right side was involved 331 times and the left 307. In single lobe infections the right lower and left lower were implicated with about equal frequency. In two lobe infections the combination of right and left lower lobes was by far the commonest.

The lobes involved in the pneumonic process are larger than the unaffected lobes and fill up the greater part of the pleural space. The affected lobes are congested and covered with a deposit of fibrin, and on palpation are much firmer than normal lung tissue. When consolidation is complete the lobe has a consistency very much like that of liver. The trachea and bronchi contain blood-stained, viscid sputum.

The process in the lung passes through a series of stages known as: (1) The stage of engorgement, (2) the stage of red hepatization, (3) the stage of gray hepatization, and (4) the stage of resolution. Two or more of these stages are usually demonstrable in the same case at autopsy—the reason for this being that infection starts in one lobe and, as the disease progresses, spreads to other lobes. In the parts first infected the process is naturally more advanced than in the parts last infected.

Stage of Engorgement.—This is the initial stage of the infection and is rarely seen at postmortem. The lung is still crepitant, but less so than in the healthy state. There is intense congestion of the tissue, which is heavier than normal. On section the cut surface oozes a large quantity of bloody, frothy fluid. Microscopical sections show congestion of all the blood-vessels and engorgement of the capillaries in the alveolar walls, with exudation of

plasma and red blood-cells into the alveolar spaces. During this stage there is only moderate infiltration of leukoctyes and these are chiefly in the perivascular and peribronchial lymph-spaces and in the alveolar walls. In the stage of engorgement the pneumococci are for the most part still in the interstitial tissue.

Stage of Red Hepatization.—In this stage the lobe becomes completely solidified with exudate. The surface is dark red and covered with fibrin, and the lung has the consistency of liver. On section the cut surface is also dark red and rather dry and granular. Microscopical examination now shows the alveoli filled with fibrin, in the meshes of which there are many red blood-cells and polymorphonuclear leukocytes. During this stage the cells show very little tendency toward disintegration. Many pneumococci are found in the alveoli, but phagocytosis is not active.

Stage of Gray Hepatization.—In this stage the lobe takes on a grayish-yellow color, usually mottled with patches of red. On section the cut surface is of the same shade, and on scraping the surface with a knife a thick purulent exudate is removed. The bronchi contain purulent sputum. The grayish color is due largely to the leukocytes, which in microscopic sections are found in great numbers in the alveolar spaces. The red blood-cells and many of the leukocytes are undergoing disintegration. There are still many pneumococci in the alveoli, but phagocytosis is active.

Stage of Resolution.—This stage, like the stage of engorgement, is not often seen at autopsy. When resolution is well advanced the lobe on section has a translucent jelly-like appearance and comparatively little exudate is demonstrable on the cut surface. Microscopical examination shows the alveoli to be only partially filled with cells. Most of the fibrin and red cells have disappeared and the leukocytes which survive are in various stages of disintegration. The most characteristic feature in this stage is the considerable number of desquamated epithelial cells in the alveoli and the regeneration of the epithelial lining of the alveolar walls.

Lesions in Other Organs.—The heart is filled with fibrinous coagula. The spleen usually shows moderate enlargement. The liver and kidneys are the seat of cloudy swelling. In fatal cases complicating infections of pneumococcal origin are frequently discovered in the various organs. Suppurative pleuritis and pericarditis, endocarditis, meningitis, and arthritis are among the commoner complications encountered.

Experimental Pneumonia.—Various investigators have produced pneumonia experimentally in animals by injecting pneumococci directly into the trachea and bronchi. It is rather difficult to reproduce perfectly the pathological and clinical picture of lobar pneumonia in ordinary laboratory animals. In monkeys, however, the disease can be perfectly reproduced by intratracheal injection with various types of pneumococci. Blake and Cecil reproduced anatomical lesions and clinical symptoms identical with those of the human disease by injecting minute amounts of virulent pneumococci into the trachea of monkeys. These investigators found that it was impossible to produce pneumonia by merely introducing pneumococci into the nose or pharynx. The larynx appears to form a barrier which prevents the passage of pneumococci into the trachea except under certain conditions.

Pathogenesis.—There are some who hold that lobar pneumonia, like certain other infections, is hematogenous in origin. The only evidence,

however, in support of such a view, is afforded by the few cases in which pneumococci have been isolated from the blood before physical signs of pulmonary involvement were present. In view of the difficulty often attending the detection of the earliest pulmonary lesions this evidence is not of great value. Furthermore, Blake and Cecil have shown that in the experimental pneumococcus pneumonia of monkeys, the pneumococci may enter the blood-stream following intratracheal injection, in some instances before the symptoms or physical signs of pneumonia have developed. Attempts to produce lobar pneumonia in animals by intravenous or subcutaneous inoculations of pneumococci have consistently failed. On the other hand, the more commonly accepted view that the mode of infection is by way of the air passages has received considerable confirmation from the experimental production of pneumococcus pneumonia in animals by intratracheal inoculations.

Blake and Cecil have also studied the mode of dissemination of the infection in lobar pneumonia. They found that when virulent pneumococci were injected into the trachea of monkeys the bacteria usually invaded the pulmonary tissue at some point or points in the portion of the lobe proximal to the hilum, that they spread rapidly throughout the lobe by way of the peribronchial and septal interstitial tissue and lymphatics, and that they finally invaded the alveolar structure primarily by way of the alveolar walls, subsequently passing into the alveolar spaces simultaneously with the outpouring of exudate into the alveoli. In other words, lobar pneumonia is primarily an interstitial infection of the lungs, the exudate appearing subsequent to the interstitial infiltration. Blake and Cecil found that in some infections in monkeys the process remained largely interstitial throughout the disease and similar findings have been occasionally noted in man.

Chemical Changes in the Blood.—Inasmuch as the lungs are constituted to absorb oxygen and eliminate carbon dioxid, it is evident that a disease with wide-spread involvement of these organs is apt to result in disturbance of these functions. As far as carbon dioxid is concerned, the evidence bearing on failure of elimination is far from definite. Lowering of the alkaline reserve has been frequently reported, but only occasionally of more than moderate severity, whereas an actual shift of the H-ion concentration of the blood to the acid side is a rare occurrence.

It has recently been shown, however, that there may occur a deficiency of oxygen of such severity as to result in a fatal outcome of the disease before the struggle between the forces of immunity has been decided. Cyanosis has long been *prima facie* evidence of the existence of oxygen deficiency, but it has been only in recent years that the recognition of arterial anoxemia in quantitive terms has led to an understanding of its importance. With the introduction of the arterial puncture by Huerter and Stadie, the discovery of severe oxygen deficiency in the arterial blood of patients with pneumonia made possible the application of the physiology of "oxygen want," previously worked out by Haldane, Barcroft, Schneider, and others.

The arterial blood is normally 95 per cent. saturated with oxygen. In severe cases of pneumonia saturation of only 75 per cent. is not uncommon. When the blood of a normal individual is lowered to this extent by breathing atmosphere low in oxygen a train of harmful symptoms becomes manifest. The pulse rises approximately from 72 to 120, the patient breathes with increased rapidity, shallowness, and difficulty, becomes irrational, suffers

from nausea, vomiting, and at times visual disturbances, and feels weak and sick. More severe anoxemia brings about coma, heart failure, and death. Mountain sickness and carbon monoxid poisoning are clinical examples of illness due *purely* to oxygen want, in the latter case frequently fatal. In pneumonia the symptoms of anoxemia are added to the symptoms due to the infection. It is thus evident that the degree to which arterial anoxemia may occur in pneumonia is productive of decidedly injurious effects.

Other Chemical Changes in the Blood.—There is considerable retention of chlorids during the active stage of pneumonia, but this retention is not accompanied by an increase of chlorids in the blood. There is also a definite increase in the amount of circulating fibrinogen.

Symptoms.—The symptoms of lobar pneumonia vary somewhat with the age of the patient and the type of micro-organism concerned in the infection. There is no single symptom that is present in every case. In the great majority of instances, however, the clinical picture is quite typical; indeed, there is perhaps no infectious disease in which it is so characteristic.

General Description.—*Period of Incubation.*—The period of incubation is usually short, probably not over twenty-four or forty-eight hours. Once the pneumococcus has gained access to the bronchial tree it soon penetrates the mucous membrane and gets into the lymphatics, where it spreads with great rapidity. In the experiments of Blake and Cecil symptoms of infection appeared in the monkeys eight to twelve hours after intratracheal injection.

Onset.—The onset may be sudden or gradual. Prodromal symptoms of malaise may be present, but many patients insist that they have been perfectly well up to the moment acute symptoms appear. The individual, for example, goes to bed feeling perfectly well, to be awakened in the night with a hard shaking chill or a sudden attack of sharp pain in the side. A majority of patients give a history of having had a mild infection of the nose or throat preceding the onset of acute symptoms. In the Bellevue Hospital series 32.5 per cent. gave a history of preceding respiratory infection. This figure is probably much too low. A more careful inquiry on this point would probably have elicited a history of preceding infection in 60 or 70 per cent. In the Rockefeller Institute series Cole reports 40 per cent. giving a history of previous cold, sore throat, or other respiratory disease. In the Bellevue Hospital series it was observed that *primary* pneumonia was more common in the case of Type I and Type II infections, while pneumonia *secondary* to other infections was more frequently due to pneumococcus Type III, Type IV, or streptococcus.

The cardinal symptoms of pneumonia are chill, fever, pain in the side, cough, and the expectoration of rusty sputum. Dyspnea is also a frequent symptom in the early stage. The patient, when seen twelve to eighteen hours after the chill, is acutely ill. One or both cheeks are flushed, and the temperature is 103° to 104° F. The respiration is rapid, often painful, on account of the pleuritic irritation. The patient coughs frequently and may bring up a small amount of rusty sputum. Even when actual pain is absent the breathing is embarrassed. Herpes is often present on the lip and the tongue is heavily coated. If the temperature reaches 104° or 105° F., the patient may become delirious. These symptoms continue without much change for five to ten days. In a majority of cases the disease then termi-

nates rather abruptly by crisis or lysis; in the remainder, the patient dies from sepsis or toxemia, or from some complication.

Symptoms in Detail.—The chill is one of the most characteristic features of lobar pneumonia and is usually the first symptom to make its appearance. A definite chill occurs, however, in only two-thirds of the cases. Other patients note only chilly sensations. In the Bellevue series the incidence of chill was somewhat higher in the Type I and Type II pneumonias than in the other types. The chill may be mild or severe and usually lasts fifteen to thirty minutes.

Pain in the side is also a very common symptom, usually appearing shortly after the chill. In some cases it precedes the chill, and in still others the chill is absent and the disease is ushered in by the pain in the side. In the Rockefeller Institute series 75 per cent. of the patients gave a history of

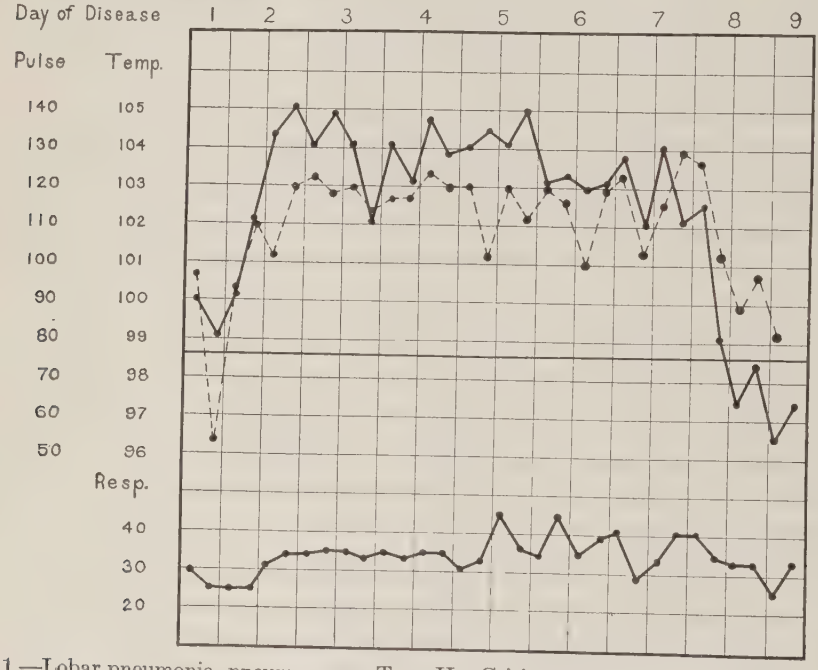

Fig. 1.—Lobar pneumonia, pneumococcus Type II. Crisis on eighth day. Pulse curve indicated by dashes.

pain in the side, and in the Bellevue Hospital series an almost identical number presented this symptom. The pain is usually located in the region of the nipple or at the base of the affected lung, but in some cases it is referred to the abdomen and is accompanied by abdominal tenderness suggestive of appendicitis, cholecystitis, or general peritonitis. In upper lobe infections pain may be absent or referred to the shoulder.

The *temperature* rises rapidly during the chill and thereafter usually remains high, ranging between 103° and 105° F. In the fixed types of pneumonia the temperature is apt to run along without much variation on a high plateau. In Type IV infections the temperature is often irregular, in this respect resembling streptococcus pneumonia. In very old persons the temperature is much lower and may run an almost normal course. The

fever is not a very reliable guide as to the seriousness of the infection; indeed, there is some evidence to show that a high fever is a distinct advantage to the patient in his struggle with the disease.

At the time of onset the *cough* is of a dry, hacking character unless the condition has been preceded by bronchitis, when the sputum may be of a distinctly purulent character. The cough is apt to come in paroxysms and causes the patient much pain when accompanied by pleurisy. As the disease progresses the cough becomes less painful and more productive. The expectoration in pneumonia is one of the most characteristic symptoms; the typical rust-colored sputum is pathognomonic and the diagnosis of lobar pneumonia can safely be based on the finding of such expectoration. The character of the sputum changes as the disease progresses. From being pinkish or blood-streaked at the very beginning, it becomes rusty and viscid on the third or fourth day. At this time it has a lemon, orange, or brownish-red color like that of fresh iron rust. As the disease passes into the stages of gray hepatization and resolution, the sputum becomes yellow and mucopurulent. Microscopically the sputum contains mucus, red blood-cells, pus-cells, epithelium, and usually a considerable number of pneumococci.

The Circulatory System.—The *pulse* is nearly always rapid and in proportion to the degree of fever. During the early stage the pulse is sometimes dicrotic, but not so frequently as in typhoid fever. Irregularity of the pulse may occur as a result of toxemia or from the administration of digitalis. In a case of Type I pneumonia observed by the writer, auricular fibrillation was present, but disappeared promptly after the administration of antipneumococcus serum. Extrasystoles are quite commonly observed, especially in patients who are receiving digitalis.

The *blood-pressure* usually maintains a normal level, but is apt to fall if the patient begins to lose ground. In our experience a systolic blood-pressure below 100 is a rather serious prognostic sign.

Cyanosis is an important symptom of lobar pneumonia, and is present to some degree in almost every case. Cyanosis is most marked in the severe infections, usually where several lobes are involved. The cyanosis is due to incomplete saturation of the blood with oxygen which, in turn, is dependent upon pathological changes in the lung or some disturbance, such as shallow breathing, in the respiratory mechanism. It has also been shown that cyanosis in pneumonia is related to the change of hemoglobin into methemoglobin by the pneumococcus.

The *heart* usually shows some enlargement, particularly the right side, by reason of the extra burden placed upon it in forcing blood through the congested lungs. The second sound over the pulmonic area is accentuated, and a soft systolic murmur may be heard at the apex. The heart may be slightly displaced by a massive consolidation of one lung. As the myocardium becomes exhausted by the toxemia and additional strain, the heart sounds become less distinct and may take on a fetal character (embryocardia).

The Blood.—A polymorphonuclear leukocytosis occurs in a large proportion of cases. The count varies from 10,000 to 40,000, depending to some extent on the day of the disease. In the Bellevue Hospital series the highest counts were usually observed during the first forty-eight hours of the disease, and similar findings were obtained in the experimental pneumonia of monkeys. As a general rule, a high leukocyte count is a good prog-

nostic omen. According to Osler, the blood-platelets are greatly increased in number.

Dochez found that the coagulation time of the blood is usually prolonged during the acute stage of pneumonia. There is also an increase in the quantity of circulating fibrinogen. Palmer has shown that there is an increase of excretion of total acids in the urine in pneumonia, not sufficient in amount, however, to indicate that any marked degree of acidosis exists.

Bacteriemia.—Pneumococci can be demonstrated in the blood in approximately one-third of all cases of lobar pneumonia. The significance of bacteriemia is more grave when it occurs late in the disease than when it occurs early. Under any conditions, however, it indicates a severe infection, and is usually observed in connection with extensive involvement of the lungs. Patients with pneumococcus septicemia are more apt to present symptoms of anoxemia than are those in whom the blood culture remains sterile.

Respiratory System.—The respirations are hurried and shallow. The respiratory rate is practically always increased out of proportion to the degree of fever. Indeed, this is a significant point in distinguishing pneumonia from other febrile conditions. The respirations usually run 25 to 40 a minute, but may be even more when there is pain in the side or a marked grade of anoxemia. A characteristic feature of the respiration is the peculiar expiratory grunt. Inspiration is usually accompanied by dilatation of the alæ nasi. As the respiratory rate increases the volume per respiration decreases.

The rapid respiration is practically always accompanied by *dyspnea*, which increases in proportion to the amount of lung involved and decreases at the time of crisis, although the lung is still consolidated. The dyspnea of pneumonia is probably referable to a number of causes, among which may be mentioned diminution in breathing capacity, pleuritic pain, shallow respiration, and cardiac embarrassment.

The Urine.—In pneumonia the urine is scanty, high colored, and of high specific gravity. It usually contains a trace of albumin, and in many cases casts also. These findings, however, as in many other fevers, simply indicate a toxic irritation of the kidneys. Another interesting feature of the urine is the great decrease in the content of chlorids. As much as 10 grams of sodium chlorid may be retained in the body during the course of the disease. During convalescence there is usually an increased excretion of chlorids.

Nervous Symptoms.—Delirium is present in approximately 25 per cent. of cases. It is particularly common in alcoholic patients, who frequently must be forcibly restrained to prevent their getting out of bed. Heavy drinkers often develop symptoms of delirium tremens during the course of pneumonia, a complication which renders the prognosis very grave. In mild cases it is not unusual for the mind to remain clear during the entire course of the disease. In children the disease may be initiated by a convulsion and other cerebral symptoms strongly suggestive of meningitis. In the series at Bellevue Hospital several patients developed a post-pneumonic psychosis in the form of a confusional insanity, which, however, in every case terminated favorably after a short time.

Hemiplegia occurring in the course of pneumonia may be due to thrombosis or embolism or, in rare instances, to a brain abscess.

Gastro-intestinal Symptoms.—Jaundice occurs in 5 to 10 per cent.

of cases. It has no bearing on the prognosis. Herpes is observed in more than half the cases. It usually occurs on the lips, but is sometimes seen on the nose or cheek. The writer recalls one patient in Bellevue Hospital with a herpetic eruption that covered almost one-half of the entire face. Nausea and vomiting are fairly frequent symptoms of pneumonia. In some cases the illness is ushered in by an attack of vomiting. Diarrhea is an unusual symptom.

Tympanites is frequent and troublesome and is most marked in the severe cases. It may be merely an expression of gastro-intestinal disturbance, but is more frequently the result of general toxemia. When marked, it may add considerably to the respiratory embarrassment.

Physical Signs.—The physical signs in a typical and fully developed case of lobar pneumonia are quite characteristic, but during the first twenty-four or forty-eight hours of the disease they may be almost, if not entirely, lacking. With the development of specific treatment the early diagnosis of lobar pneumonia becomes more and more important, and a careful search for the earliest physical signs is imperative.

Physical Signs at Onset.—The face is flushed, often cyanotic. The breathing is usually labored on account of the pain in the side, and even at the onset herpes may be present on the lips; there is a dry, hacking cough and the nostrils dilate with inspiration. Frequently the patient gives a little grunt with each expiration. Examination of the chest reveals restriction of movement on the affected side. In the early stage palpation or percussion are usually negative, or there may be only slight dulness at one base. Pain in the side usually calls special attention to the lobe affected, and auscultation over this area often reveals a characteristic feature of the early stage; namely, *quiet* or *suppressed breath sounds*. Over the same area another early sign, heard at the end of inspiration, is the shower of fine crepitant râles due to congestion and edema of the air-cells. Tubular voice and breath sounds are rarely heard during the first few hours of the disease.

Physical Signs in a Well-developed Case.—By the second or third day the typical physical signs of lobar pneumonia are usually present over one or more lobes. Inspection shows signs similar to those just described under onset, but more intensified. The patient looks sicker and cyanosis and dyspnea are more marked. The cough is no longer dry and hacking, but is accompanied by viscid expectoration which is usually rusty in character. Examination of the patient reveals much less movement on the affected side. The respiration is rapid and accompanied by auxiliary action of the accessory muscles. According to Osler, mensuration may show a definite increase in the volume on the side affected, rarely more, however, than 1.5 or 2 cm. On *palpation* a pleural friction-rub may sometimes be felt. The most important information obtained, however, on palpation is the greatly increased vocal fremitus on the affected side. This important sign is sometimes masked by an accumulation of sputum in the main bronchus. This difficulty, however, can be overcome by having the patient cough before examination.

Percussion.—In the well-developed case percussion reveals dulness over the affected area. In some instances the note may become almost flat, differing very little from that obtained over a pleural effusion. Over the uninvolved tissue just above a consolidated area percussion may elicit a note of tympanitic quality usually referred to as Skoda's resonance.

Auscultation.—As frank consolidation develops, the fine crepitant râles disappear and the normal vesicular breathing is replaced by tubular breath sounds. This tubular breathing is very characteristic—high pitched, rather harsh, and with expiration of equal length with inspiration. As in the case of vocal fremitus tubular breathing may be absent when the larger bronchi are completely plugged with exudate. The voice sounds as well as the breath sounds have a frankly bronchial quality usually spoken of as bronchophony. In certain cases the bronchial voice sounds may have a nasal quality as well, a condition which is termed *egophony*. The whispered voice is also much intensified over the consolidated area.

Physical Signs During Resolution.—The patient looks and feels more comfortable and the cyanosis is much less marked. The temperature and pulse are lower and the respiration is not so rapid. The cough is less distressing and is accompanied by expectoration of considerable thick yellow sputum. The area of dulness begins to decrease in size and auscultation over this area reveals many moist râles of the subcrepitant and mucous type. As resolution progresses still more, the voice and breath sounds over the affected area lose their tubular quality and return to normal.

Course and Termination.—The fever persists for from five to ten days, sometimes even longer. During this time the temperature is often remarkably constant, varying between 104° and 105° F., for day after day. In old people the temperature is frequently lower and more irregular than in children and young adults.

Pneumonia may terminate by crisis or lysis. The typical crisis of pneumonia is one of the most striking features of the disease. The patient, struggling against a virulent infection, often appears on the verge of collapse. The whole organism seems to be affected by the toxemia. Suddenly the patient begins to perspire freely; there is a rapid drop in temperature to normal or subnormal, accompanied by a corresponding fall in the respiration and pulse rate. In a few hours the entire clinical picture is changed. The patient looks and feels much better and drops off into a quiet sleep. In some cases the true crisis is preceded by the so-called pseudocrisis. The temperature drops to normal or almost normal, then rises again to 102° or 103° F. for twenty-four hours, when the true crisis occurs.

In a majority of cases there is no definite crisis, but the patient's temperature comes down gradually by lysis. Both crisis and lysis appear to be an expression of acquired immunity on the part of the patient. This opinion is corroborated by the fact that the various immune bodies make their appearance in the blood of the patient at the time of crisis or just after it.

In cases that terminate fatally the temperature remains high, the pulse becomes rapid and weak, and the respiration rate is accelerated. These phenomena are referable usually to *spread* of the pneumonic process from one lobe to another until three, four, or even all five lobes are involved in the infection. The cyanosis becomes more marked, and the patient shows every evidence of an extreme toxemia. Blood-cultures taken at this time are usually positive, and in most instances there is a drop in the leukocytic count. The immediate cause of death in pneumonia has been much debated. In a majority of cases some form of circulatory failure is undoubtedly responsible for death, but whether this failure is in the heart muscle or is the result of vasomotor paralysis is not easy to determine. In some cases death appears to be referable to respiratory failure. Various complications traceable to

pneumococcal origin, such as endocarditis, pericarditis, and meningitis, are the immediate cause of death in not a few cases.

Complications in pneumonia are numerous but, as a rule, they are not so serious as those encountered in typhoid fever. They may be divided into two groups—those that are directly referable to the pneumococcus, and those which appear to be of toxic or other origin.

Acute fibrinous pleurisy occurs so frequently in pneumonia that it can hardly be called a complication. The characteristic friction-rub of dry pleurisy is noted in a good many cases early in the disease and often causes the patient great discomfort. Later on the fibrin may form a thick tenacious layer over the entire surface of the affected area.

Pleurisy with Effusion.—Acute serofibrinous pleurisy is also a common complication of pneumonia. It was present in 4.5 per cent. of the Bellevue Hospital series. It may develop early in the disease, but is more apt to make its appearance after the crisis. The presence of a pleural effusion is usually indicated by some rise in temperature, but not necessarily. The physical signs are those of fluid in the chest. If any considerable amount of fluid collects, it should be aspirated.

Empyema is perhaps the most frequent complication of lobar pneumonia. In the Bellevue Hospital series 7.1 per cent. developed empyema. This incidence rate is higher than that of most authors, due no doubt to the fact that in the Bellevue series many of the fatal cases were subjected to necropsy or to exploratory thoracentesis. The incidence of empyema was almost the same for all pneumococcus types, as the following figures show:

	Cases.	Percentage with empyema.
Pneumococcus Type I	346	7.5
Type II	165	6.0
Type III	137	8.0
Type IV	263	6.8
Streptococcus hemolyticus	53	33.9

Occasionally empyema of *Streptococcus hemolyticus* origin complicates a pneumococcus pneumonia, but this is rather rare.

Pneumococcus empyema usually develops after subsidence of the more acute symptoms of pneumonia. In the Bellevue Hospital series 81.7 per cent. of empyemas developed after the seventh day of the disease. On the other hand, 67.6 per cent. of streptococcus empyemas developed before the seventh day. Empyema should be suspected in any case in which after several days of normal temperature a fever of several degrees again makes its appearance, accompanied by increase in pulse and respiration rate and by a polymorphonuclear leukocytosis. Physical examination reveals the signs of fluid—absence of vocal fremitus, flatness on percussion, and diminished voice and breath sounds. Sometimes a pocket of pus develops between two lobes. This is known as *sacculated empyema*, the diagnosis of which is somewhat difficult. The diagnosis is also obscure in those cases in which the amount of pus is very small. In most cases *x*-ray or fluoroscopic examination and exploratory aspiration determine the diagnosis.

The seriousness of empyema depends largely on when it develops. If it appears early in the course of pneumonia, the prognosis is grave. On the other hand, the development of empyema a week or ten days after crisis is usually a comparatively mild complication. The early cases are treated

first by aspiration, but sooner or later both early and late cases require thoracotomy, including rib-resection and drainage.

Suppurative pericarditis is another one of the more serious complications of pneumonia. It occurred ten times in 1082 pneumonias in the Bellevue Hospital series. These figures do not, of course, include dry pericarditis, which is also a common incident in the course of pneumonia and of comparatively little clinical significance. All 10 of the patients with suppurative pericarditis died. In our experience, pericarditis was associated with empyema in all but one of the cases, and in all but one was caused by the pneumococcus.

Pneumococcus endocarditis is a rare complication. It occurred only six times in 1082 patients with pneumonia in Bellevue Hospital. This condition may develop during the course of the pneumonia, or come on gradually several days after the temperature has been normal. It is more likely to occur in patients with chronic valvular disease. Like other types of malignant endocarditis, it runs a swift septic course, with irregular temperature, rapid pulse, and often chills and sweats. In the experience of the writer, it has been invariably fatal. The lesions are chiefly on the mitral valve, though other valves may be involved. Physical examination reveals a blowing systolic murmur which increases in intensity as the disease progresses. The signs of embolism in the various organs appear from time to time.

Meningitis, like pericarditis, is rare, but invariably fatal. In Bellevue Hospital meningitis occurred in 19 cases, an incidence rate of 1.8 per cent. It is often associated with endocarditis and practically always with pneumococcus septicemia.

Pneumococcus arthritis is a rare complication. It develops only in cases with pneumococcus septicemia. The condition is usually monarticular and generally takes on the character of a surgical joint. In some cases, however, the joint does not suppurate and the condition clears up spontaneously.

Thrombosis and *embolism* are both rare complications and usually occur in the femoral vessels.

Pneumococcus peritonitis occurred in only two of the Bellevue cases. Both patients died.

Pneumococcus abscesses of the skin are occasionally observed, but usually skin infections encountered in pneumonia are of staphylococcal origin.

Associated Conditions.—In addition to the above described pneumococcus complications, there are a number of other conditions frequently seen in association with lobar pneumonia.

Lung abscess is not so common in lobar pneumonia as is generally supposed. When present it is usually due to bacteria other than the pneumococcus.

Gangrene is a complication seen mostly in old patients. It is very often associated with abscess of the lung. The diagnosis can usually be made from the fetid odor and dark green color of the sputum. The condition is invariably fatal.

Acute Nephritis.—Many patients show signs of renal irritation, such as the presence of albumin and casts in the urine, but genuine nephritis is a rare complication.

Parotitis occurred in 10 of the Bellevue cases, and in those where cultures were taken the infection was of staphylococcal origin. Osler says

parotitis is commonly seen in association with endocarditis, where it is presumably a pneumococcus infection. This does not agree with our experience, though it has usually occurred in severe types of pneumonia. The death rate in the Bellevue cases was 70 per cent. In our series drainage by massage has given better results than surgical intervention.

Otitis media is not an infrequent complication in children.

Massive collapse of one or more lobes of the lung, due to obstruction of a bronchus with mucus or sputum, is a rare and serious complication.

Unresolved Pneumonia.—Delayed resolution is one of the sequelæ of pneumonia which may occur at any age, but is seen chiefly in elderly patients. The temperature returns to normal or almost normal, but the signs in the chest persist. In the average case of pneumonia the signs in the lungs usually clear up completely within a week or ten days after crisis. From observations made by the writer on monkeys convalescing from experimental lobar pneumonia, complete restoration of the lung to normal is probably a matter of several weeks. Physical signs, however, disappear some time before resolution is complete. In the Johns Hopkins Hospital series of Osler, 3 to 4 per cent. of patients showed delayed resolution. In most cases the signs persist for two or three weeks, but in some instances they may continue for two or three months. During this period the temperature is normal, or only slightly elevated. The patient has no particular discomfort, but the strength and weight do not return to normal. Physical examination shows bronchial breathing associated with moist râles. Sometimes the bronchial breathing disappears and only the dulness and râles persist. Most of these patients eventually recover.

Chronic Interstitial Pneumonia.—Occasionally a patient with delayed resolution fails to recover and the condition passes over into a chronic interstitial pneumonia, the symptoms of which are described elsewhere.

Relapses and Recurrences.—Relapse is not common in pneumonia, though it does occur. Subsequent to the first attack the temperature may remain normal from one to ten days, or even two weeks. Relapses in pneumonia are usually, but not always, caused by a type of pneumococcus different from that of the first attack. The severity of the relapse naturally depends on the character of the second infection. Relapses are usually seen in hospital practice, where the new infection is picked up from some neighboring patient. Streptococcus hemolyticus pneumonia secondary to pneumococcus pneumonia was frequently observed in the army. Relapses of streptococcic origin are more serious than those due to the pneumococcus. We have seen quite a number of relapses in pneumococcus Type I infections that received specific therapy in inadequate dosage. In such cases the second attack was also of Type I origin.

Recurrence is more frequently observed in pneumonia than in any other acute infectious disease. By reason of this fact the impression prevails that one attack actually predisposes to another. There are cases in the literature of patients who have had twenty or thirty attacks of the disease. In the experience of the writer recurrences have usually been due to different types of pneumococcus or at least to different varieties of pneumococcus Type IV. We know of several individuals who have experienced repeated attacks of pneumococcus Type III pneumonia. In such cases a chronic focus of infection, possibly in one of the sinuses, should be looked for.

Special Varieties of Pneumonia.—Abortive Pneumonia.—Pneumonia

occasionally runs a very short course. The writer has seen one twenty-four-hour pneumonia and several forty-eight-hour cases. The early administration of serum in Type I cases often produces this clinical picture. In such cases the signs are apt to be localized over a small area.

Central Pneumonia.—In these cases the area of consolidation is situated near the hilum and frank physical signs are not present. The fluoroscope is of great assistance in the diagnosis of such conditions.

Pneumonia in the Aged.—The onset is often insidious and the temperature may be normal or only slightly elevated. The physical signs may be frank or very indefinite. These patients often die suddenly of heart failure several days, or even two weeks, after all signs of pneumonia have disappeared. A large proportion of senile pneumonias fall in the pneumococcus Type III or Type IV groups (80 per cent.).

Pneumonia in Infants.—All types of pneumococcus pneumonia occur in infants, but Type IV infections are the most common. The death rate is high in infants under two years of age. In children over two years of age lobar pneumonia usually runs a mild course. Meningeal symptoms are often prominent in the pneumonia of infants.

Pneumonia Secondary to Other Diseases.—A terminal lobar pneumonia is seen very frequently in the course of chronic cardiac and renal disease, diabetes, pernicious anemia, etc. In the Bellevue Hospital series 14.3 per cent. of the cases occurred subsequent to some chronic systemic disease. The death rate in these cases was approximately 50 per cent.

Lobar pneumonia is frequently seen as a complication of other infectious diseases, particularly influenza and measles. The lobar type of secondary pneumonia is nearly always of pneumococcal origin. Bronchopneumonia is often caused by the streptococcus or the influenza bacillus. The writer has been struck with the rarity of lobar pneumonia as a complication of chronic pulmonary tuberculosis. These patients often die of bronchopneumonia, but true lobar pneumonia is unusual.

Postoperative pneumonia is a secondary pneumonia due either to the aspiration of mucus and saliva into the air passages or to the irritating effect of the anesthetic on the bronchial mucous membrane. A large proportion of postoperative pneumonia is caused by pneumococcus Type IV. Postoperative pneumonia usually runs a mild and rather atypical course.

Diagnosis.—In a typical case of lobar pneumonia the diagnosis can usually be made within a few hours after onset, though the characteristic physical signs may have not yet made their appearance. A patient suddenly taken with chill, fever, herpes, cough, dyspnea, and pain in the side presents a picture which can hardly be mistaken for any other condition. There are a considerable number of cases, however, usually secondary to some mild respiratory infection, in which the onset is gradual and in which the more characteristic symptoms may be entirely absent. Lobar pneumonia may develop without chill or pain in the side; even the cough and expectoration are sometimes absent. In cases of this type rapid respiration associated with cyanosis is a suggestive combination of symptoms. Indeed the respiration rate in pneumonia is nearly always out of proportion to the degree of fever. One of the most convincing evidences of lobar pneumonia is the typical rusty sputum which is practically never seen in any other condition.

It is important for the student of medicine to recognize the early symptoms and signs of pneumonia in order that specific treatment may be applied

promptly. Slight dulness, a few moist râles, and diminished breath sounds may be the only local signs during the first twenty-four or thirty-six hours of the disease. Of these signs, suppressed breathing is perhaps the most important. By the third day frank signs of consolidation are usually present—increased vocal fremitus, dulness, and bronchial voice and breathing.

The laboratory aids in the diagnosis of lobar pneumonia are: (1) the leukocyte count, (2) *x*-ray examination, (3) bacteriological examination of sputum, and (4) the blood-culture.

1. The leukocyte count is usually elevated during the first two or three days, even in those cases that later develop a leukopenia. Only in the most fulminating infections is leukopenia present from the very onset. The differential count shows a polyneucleosis of 80 to 90 per cent.

2. Radiographical or fluoroscopical examination may be of great help in the early diagnosis of pneumonia or in verifying the diagnosis in doubtful cases. As one would expect from experimental studies in monkeys, the consolidation begins at the hilum and rapidly spreads outward to the periphery.

3. When the clinical diagnosis of lobar pneumonia has been made it is, of course, important to determine the exact character of the infection. Pneumonia may be caused by a number of different bacteria. It is extremely essential, both from the standpoint of prognosis and treatment, that the physician should know the bacteriological nature of the infectious process. In the first place, is he dealing with a pneumococcus infection? If so, what type of pneumococcus? The bacteriological examination of the sputum usually supplies this information. Cultures may be made directly on blood-agar plates, but this method is slow and impractical. The mouse test is now looked upon as the most reliable method of determining the type of organism in pneumonic sputum. By this method a positive diagnosis can usually be made in twelve to eighteen hours. About 0.5 c.c. of washed sputum emulsified in sterile normal salt solution is injected intraperitoneally into a white mouse. The mouse is killed after twelve to eighteen hours. If pneumococcus is present, an agglutination test can be performed at once on the peritoneal exudate and the type determined. If the infectious agent be *streptococcus* or *Bacillus influenzæ*, or even *Friedländer's bacillus*, the mouse exudate will indicate it, for the peritoneum of the mouse is an ideal culture-medium for all of these bacteria. When no sputum is obtainable, mouth-washings from the patient will often give positive results.

The Krumwiede method of typing the sputum is quick and reliable, but gives information only concerning the three fixed types of pneumococcus.

The Avery method is accurate when one uses very clean sputum in which the pneumococcus is present in practically pure culture. Unfortunately, specimens of this character are not often obtained.

4. Very frequently the patient with pneumonia has no sputum during the first forty-eight hours of the disease; in other words, during the very time when a bacteriological diagnosis is most important. A blood-culture taken at this time may supply the necessary information; 5 to 10 c.c. of blood are withdrawn from a vein and cultured in broth and on agar plates. If pneumococcus is present, the type may be determined at once by the agglutination test.

Precipitin Test on Urine.—When sputum is not obtainable the identification of the fixed types of pneumococcus can sometimes be made very

promptly by a precipitin test on the urine. Positive reactions, however, are usually obtained in severe cases only.

Differential Diagnosis.—*Pleurisy* is often confused with pneumonia, especially when there is pleural effusion. In both pneumonia and in pleurisy the affected side shows some degree of immobility, and there is dulness on percussion, but in pneumonia the intercostal spaces are not obliterated, the heart is rarely displaced, and the dulness is not so absolute. Most important of all, vocal fremitus is decreased or absent in pleurisy with effusion, while in pneumonia it is intensified. In pneumonia the voice and breath sounds are loud and tubular; in pleural effusion the voice and breath sounds are diminished. In children, however, pleural effusion may present nearly all the signs of a pneumonic consolidation. It must not be forgotten that pneumonia and pleurisy may coexist.

Bronchopneumonia is often difficult to distinguish from lobar pneumonia. Indeed, there are many cases in which the distinction is impossible. In bronchopneumonia, however, the onset is usually more gradual, the temperature is irregular and not so high, and the physical signs are much more diffuse and indefinite.

Tuberculous pneumonia of the lobar type closely resembles lobar pneumonia of pneumococcal origin in the character of the onset, symptoms, and physical signs, and in many cases it is impossible to distinguish between the two conditions until a week or two has elapsed. The history of pre-existing tuberculosis, involvement of the upper lobes, and the history of a chronic illness suggest tuberculous pneumonia. A high leukocyte count may be seen in both conditions. Sooner or later the patient expectorates large quantities of purulent sputum in which tubercle bacilli can readily be demonstrated.

Pulmonary infarction may simulate lobar pneumonia, especially when the infarct is of considerable size. In patients with chronic cardiac disease the diagnosis of lobar pneumonia should never be made until pulmonary infarction has been excluded. The latter condition is not so apt to be ushered in with a chill, the fever is not so high, and there is little, if any, change in the blood-count. In pulmonary infarction the sputum is bloody rather than rusty. Pulmonary infarcts sometimes become infected and develop into frank pneumonic processes.

Lobar pneumonia is sometimes mistaken for *appendicitis* and *cholecystitis* in those cases where diaphragmatic pleurisy is present. In such cases the pain is referred to the abdomen and there may be considerable abdominal tenderness and rigidity.

Prognosis.—The prognosis in pneumonia depends upon a great many factors. It is considered the most serious of the commoner acute infectious diseases that occur in the temperate zone. In the large city hospitals of both Europe and America the death rate is usually in the neighborhood of 30 per cent. In Bellevue Hospital the records show that the death rate has varied considerably from year to year, ranging from 30 to almost 50 per cent. The death rate has been distinctly lower since 1919—a fact which is rather difficult to explain. Prohibition, the great influenza epidemic, and the improved conditions of living are possibly all factors.

The death rate in private practice is distinctly lower than that in hospitals. Most of the series, however, reported from private practice are not large. If one includes senile and terminal pneumonias, the death rate, even in private practice, must be very close to 25 per cent.

Effect of Age on Prognosis.—Youth is the greatest of all assets in lobar pneumonia. In children between two and ten years old the death rate is under 10 per cent., and the figure is little, if any, higher for patients in the second decade of life. In hospital practice the mortality rate tallies almost exactly with the age of the patient, that is, 20 per cent. between the ages of twenty and thirty, 30 per cent. between thirty and forty, etc. In patients above eighty very few survive the disease.

Type of Infection.—The investigations of Cole at the Rockefeller Institute first showed the relation of pneumococcus type to the death rate in lobar pneumonia. Cole's figures for the four types are as follows:

	Per cent.
Pneumococcus Type I	25–30
Type II	25–30
Type III	45–50
Type IV	15–20

In the Bellevue series the death rates for types differed somewhat from the figures of Cole:

	Cases.[1]	Deaths.	Death rate.
Pneumococcus Type I	175	41	23.4
Type II	76	31	40.7
Type III	60	24	40.0
Type IV	136	31	22.8

The high death rate in Type III pneumonia can be explained in part by the fact that this infection occurs mostly in middle-aged and elderly people. In the Bellevue series the death rate for pneumococcus Type III pneumonia in patients under thirty years of age was only slightly higher than that for the other types.

Extent of Infection.—The prognosis in lobar pneumonia is much less serious when the infection remains localized in one lobe. In the writer's series of cases the death rate in one-lobe infections was only 14 per cent., while that for multilobar infections was 34 per cent.

Invasion of Blood by Pneumococci.—Septicemia may occur in pneumonia of any type and always renders the prognosis much more serious. In the Bellevue series the death rate was almost seven times as high in the cases with septicemia as in those where the blood remained sterile. The exact figures were as follows: In 111 cases that recovered only 5.4 per cent. showed positive blood-cultures. In 54 fatal cases 57.4 per cent. showed a pneumococcus septicemia. The death rate for cases that developed septicemia was 83 per cent.; for cases with sterile blood, only 17 per cent. Septicemia is so commonly associated with fatal lobar pneumonia that the patient's chances for recovery might almost be said to depend on the prevention or relief of this condition. Cole has shown that the *number* of bacteria in the blood is also of prognostic significance. The heavier the septicemia, the more grave the prognosis.

Precipitin Reaction in the Urine.—In severe pneumonia the specific precipitins appear in the urine. These bodies can rarely be demonstrated in the urine of mild cases; their presence, therefore, indicates a serious infection.

Other Factors in Prognosis.—Race and sex appear to have very little influence on the death rate in pneumonia. It has been claimed that the death rate is higher for the negro than for the white race, but these figures have been questioned.

[1] None of these patients received specific treatment.

Season appears to have some effect on prognosis. In the Bellevue Hospital series the death rate was 5 per cent. lower during the summer and fall months than during the winter and spring months.

Habits.—It is needless to say that a patient's habits play an important part in prognosis. Alcohol is particularly injurious. In the writer's series the death rate from pneumonia in alcoholics was 56 per cent., almost twice as high as that for the cases in which alcoholism was not a factor. Patients in good physical condition have a much better chance than those who have been exhausted or worn out by some previous illness. For this reason the patient's condition in life is also significant. Patients in the better walks of life, being well fed and clothed and usually in good physical condition, are a better risk than those who are poor, underfed, and ill clothed.

Treatment.—The treatment of lobar pneumonia is governed by the same general principles that apply to the treatment of all serious infectious diseases. The treatment is concerned with (1) relief of distressing symptoms; (2) general care of the patient himself, and (3) measures for destroying the infectious agent.

Symptomatic treatment may be entirely unnecessary in the milder infections, but in severe cases the control of symptoms becomes one of the physician's most important duties. Relief of pleuritic pain is one of the first problems that arises. The pain is sometimes relieved by counterirritation in the form of an ice-bag or hot poultice. Cole recommends a chest binder as preferable to adhesive plaster for immobilizing the chest. Codein ($\frac{1}{2}$ to 1 grain by mouth) is often helpful, but in cases where the pain is very severe morphin sulphate ($\frac{1}{4}$ grain hypodermically) should be used without hesitation, not only to relieve the pain, but to give the patient rest and sleep. The former prejudice against the use of morphin in pneumonia was probably not justified. Most modern writers on the subject look upon morphin as perhaps the most important remedy at hand for controlling pain, restlessness, delirium, and other untoward symptoms. Cough is often a troublesome symptom, and, like pain, is best controlled by codein or morphin. Some practitioners advocate ammonium chlorid in cases where the sputum is scanty. Restlessness and insomnia may be relieved with sulfonal or trional. If the patient becomes actively delirious, morphin is preferable. Abdominal distention is a problem encountered in nearly every severe case of pneumonia. It must be attacked promptly in order to relieve the extra burden which it places on the circulation and respiration. Proper attention to the bowels will prevent the development of distention in many cases. Enemas are preferable to cathartics. The writer prefers a soapsuds enema once every twenty-four hours. When distention develops the enemas must be supplemented by turpentine stupes and hypodermic injections of pituitrin in doses of 0.5 to 1 c.c. It is also advisable to insert a rubber tube into the rectum to facilitate the passage of gas. Hyperpyrexia and the delirium which often accompanies it may be relieved to some extent by sponge baths. Cyanosis and dyspnea are still treated in some clinics by venesection, but this mode of treatment is rapidly passing out of vogue.

Administration of Oxygen.—The rational method of treating cyanosis is by the efficient *administration of oxygen*. It has been shown that the inhalation of 40 to 60 per cent. oxygen raises the arterial saturation to or near the normal level in the majority of patients exhibiting arterial anoxemia,

and with this rise there are definite signs of clinical improvement. In a recent series of 10 severe cases of pneumonia treated in an oxygen tent Barach has noted the following beneficial effects due to the inhalation of oxygen: (1) Disappearance or diminution of cyanosis, (2) slowing of the pulse with corresponding improvement in quality, (3) slowing of the respiratory rate, (4) decreased delirium and restlessness, (5) subjective improvement. The 3 patients who died in this series all had positive blood-cultures, a circumstance which emphasizes the importance of all attempts to sterilize the blood-stream wherever possible.

The treatment of oxygen deficiency is ideally carried out by the oxygen chamber method as used by Stadie, Barcroft, and Binger, where an oxygen room encloses patient and nurse. A portable oxygen tent has been constructed by Barach and Binger which has many of the advantages of the chamber. Roth has used an oxygen head tent. Barach has devised various types of portable bedside apparatus, among which the nose-piece rebreathing apparatus is the most comfortable. In all these methods 40 to 60 per cent. oxygen is available. The nasal catheter may be made to yield 30 per cent. oxygen if 2.0 liters per minute are administered through it. The old-fashioned funnel method of giving oxygen is practically useless.

Stimulation.—The circulation must be watched for the first indications of failure. *Heart failure per se* is much less common in pneumonia than has been supposed. In a majority of the fatal cases death is referable to either respiratory failure or vasomotor paralysis. The latter is indicated by low blood-pressure, profuse perspiration, and other symptoms of shock, and is best overcome with adrenalin 0.5 c.c. every twenty minutes until six doses have been administered. After this the injections should be repeated every two hours. Digitalis is employed as part of the routine in the treatment of pneumonia at Bellevue and many other hospitals, but there is considerable doubt in the mind of the writer as to whether this procedure is necessary in every case. Digitalis is undoubtedly of great benefit where pneumonia is complicated by heart disease or cardiac irregularity, particularly auricular fibrillation. Digitalis does not increase the blood-pressure. A properly standardized tincture prepared according to the United States Pharmacopeia is the most satisfactory form for use in pneumonia. The drug is best given in doses of from 1 to 2 drams every four hours. The patient is usually digitalized by the time 3 or 4 drams have been administered. The dosage is then cut to 10 or 15 minims three times a day, just enough to keep the patient under the influence of the drug. The intravenous injection of the various preparations of digitalis is a dangerous procedure, but may be tried in acute circulatory failure. Strychnin and camphor are stimulants which have been employed considerably in the past, but are now passing out of use. Alcohol still has its advocates as a stimulant, but in the opinion of the writer it should be administered only to patients who are chronic alcoholic addicts. Caffein is a valuable stimulant and is preferred by many to adrenalin.

General Care of the Patient.—The first essential to the proper care of a patient with lobar pneumonia is good nursing. There is probably no disease in which the services of a competent, well-trained nurse are more valuable. The patient must be kept quiet and comfortable. Everything should be done to encourage sleep. The sick-room should be properly ventilated, but the patient must be kept warm and well protected from

drafts. In recent years there has been some reaction against the rigid application of treatment in the open air, regardless of the weather. Cool, bracing air is undoubtedly of value as a stimulant to the vasomotor system, but in disagreeable weather the patient is best indoors. A liquid diet is indicated, the basis of which should be milk. The writer believes that a high calory diet is not essential in the treatment of pneumonia. The disease usually runs a short course and the addition of milk sugar to the diet is apt to increase the distention. During the acute stage the patient should be forced to take plenty of fluid, particularly water—as much as 3 liters in the twenty-four hours.

Serum Treatment.—In applying specific therapy in lobar pneumonia the physician attempts, as in other infectious diseases, to confer an immediate immunity on the patient by the administration of a serum which contains in large amount the same immune bodies which the patient himself is trying to develop. Immunity against the pneumococcus is probably dependent upon a number of factors—agglutinins, precipitins, opsonins, etc.—but the most conspicuous and probably the most important of these immune substances are the so-called protective bodies. These various immune substances are all antibacterial rather than antitoxic. No toxin-antitoxin mechanism has ever been demonstrated in lobar pneumonia. These immune bodies are found in the serum of an animal that has been immunized against the pneumococcus. Protective bodies receive their name from the fact that mice, when they are injected with virulent pneumococci, may be protected from death by the simultaneous injection of a certain amount of antipneumococcus serum. Dochez established the very important fact that patients recovering from pneumococcus pneumonia develop a large amount of this protective substance against the pneumococcus at about the time of crisis or lysis.

The rational application of serum in the treatment of pneumonia dates from the separation of pneumococci into the four biological groups. Cole and his co-workers at the Rockefeller Institute immunized horses against pneumococcus Type I and Type II and tested the therapeutic value of the serum from these horses in the treatment of Type I and Type II pneumonia. In the case of Type I infections Cole found that treatment with Type I serum gave excellent results. In 195 cases of pneumococcus Type I pneumonia treated at the Rockefeller Hospital with Type I serum the mortality rate was 9.2 per cent., in contrast to the usual death rate of 25 per cent. for Type I cases that received no serum. Locke has recently reviewed the whole subject of pneumococcus Type I serum in the treatment of pneumonia. In 548 cases of Type I pneumonia treated in civilian hospitals with Type I serum the death rate was 15.7 per cent., a figure decidedly lower than the general mortality rate for cases not receiving serum. Locke emphasizes the importance of administering serum early in the disease.

The clinical effect of Type I serum on patients with Type I pneumonia is often dramatic, particularly if administered during the first twenty-four or forty-eight hours of the disease. In many instances a rapid drop of temperature occurs shortly after the injection, and this drop is accompanied by a corresponding drop in the pulse and respiration rate. The disease may terminate by crisis a few hours after the injection of serum. Cecil and Blake showed that monkeys infected with fatal Type I pneumonia could in every case be saved by the intravenous injection of Type I antipneumococcus

serum. In these experiments the serum not only lowered the temperature, but quickly cleared the blood of pneumococci.

Technic of Serum Administration.—Type I serum should be used only in the treatment of Type I pneumonia; it is, therefore, important that every case of lobar pneumonia should receive careful bacteriological study. The type of pneumonia can usually be determined most readily from the sputum, but if sputum is not available, a swab from the throat or a blood-culture will often afford the information desired. Before administering serum it must first be determined whether the patient is hypersensitive to horse-serum. The patient is questioned concerning previous attacks of asthma or hay-fever. He should also be questioned as to previous injections of immune serum for diphtheria or other infectious diseases. Finally, an intradermal skin test with horse-serum should be performed. Sterile horse-serum (normal or immune) is diluted 1 to 10 with sterile normal saline solution and 0.02 c.c. of the diluted serum is injected into the skin. A control injection of a similar amount of salt solution is also made. A positive reaction shows itself in a few minutes as an irregular wheal surrounded by a zone of erythema. If the patient is sensitive to horse-serum, he must be desensitized. In patients who are only slightly sensitive to horse-serum a subsequent hypodermic injection of 1 c.c. of horse-serum is usually sufficient to desensitize the patient. This preliminary injection should be given as a routine, as occasionally the skin test fails to show the milder grades of hypersensitiveness. If the skin test is strongly positive to horse-serum, small amounts of Type I serum must be administered subcutaneously at half-hour intervals, beginning with 0.025 c.c. and doubling the size of the dose with each injection until 1 c.c. is reached. Subsequent doses may be given intravenously at half-hour intervals, beginning with $\frac{1}{10}$ c.c. and doubling the dose at each injection. Intravenous injections must be given very slowly, and if symptoms of anaphylaxis appear, serum treatment must be suspended for several hours and then resumed at the same dosage. After 25 c.c. of serum have been given in small doses 50 c.c. may be administered, then the regular dose (100 c.c.) six to eight hours later. Desensitization is troublesome, but, fortunately, rarely necessary. Cole encountered only 2 or 3 sensitive patients in a series of over 150 cases.

Type I serum is administered intravenously by gravity or by the syringe method. It is very important that the serum be injected slowly. The introduction of the first 10 to 15 c.c. should occupy ten to fifteen minutes. During this period the patient should be carefully watched for increase in pulse rate, dyspnea, or urticaria. If these symptoms appear, it is well to stop the injection of serum for a few minutes to see if the symptoms increase in severity. They usually disappear rapidly and the treatment can be resumed. The usual dose of serum is 100 c.c. repeated every eight hours until the patient's temperature drops to 100° F. or lower and remains low. In very severe cases doses of 150 or 200 c.c. may be employed.

Serum Reactions.—The injection of serum may be followed by several types of reaction: (1) The true anaphylactic reaction; (2) the thermal reaction; (3) serum sickness.

(1) *The Anaphylactic Reaction.*—When individuals are highly sensitive to horse-serum, symptoms of anaphylactic shock may appear fifteen to twenty minutes after the introduction of serum. The patient suddenly becomes dyspneic; there is flushing of the face and asthmatic breathing,

followed by sweating, urticaria, and general anxiety. The symptoms can usually be relieved by the prompt hypodermic injection of 0.5 c.c. of adrenalin 1 : 1000 solution. Shocks of this kind occasionally end fatally, but this occurs only in cases where proper precautions have not been taken. If patients sensitive to horse-serum are properly desensitized, symptoms of anaphylactic shock will either be absent entirely or appear only in a mild form.

(2) *Thermal Reactions.*—Sometimes the injection of antipneumococcus serum is followed by a "foreign protein" reaction, which is quite different in character from the anaphylactic reaction. Thirty or forty minutes after the injection of serum the patient has a chill, which is followed by a rapid rise in temperature. The temperature remains high for several hours; then there is a rapid drop, accompanied by profuse perspiration. This type of reaction is comparatively rare after the injection of Type I serum.

(3) *Serum Sickness.*—This occurs in about 75 per cent. of all patients who receive antipneumococcus serum. The severity of serum sickness depends in part on the amount of serum administered. Symptoms usually appear seven to fourteen days after the injection of serum, though they may come earlier. The patient breaks out in a profuse urticaria, the temperature rises to 101° or 102° F., and often there is pain and swelling in various joints. These symptoms persist for a few days and then disappear.

Treatment With Solutions of Pneumococcus Antibodies.—During the last few years several derivatives from antipneumococcus serum have been prepared, which contain the protective substance, but little if any of the serum proteins. Huntoon has prepared an aqueous solution of pneumococcus antibodies which contains protective substance against the three fixed types of pneumococci. Cecil and Larsen and L. A. Conner have reported successful results in the treatment of pneumococcus pneumonia with this solution. Cecil and Larsen reported 424 cases of pneumococcus pneumonia of all types treated with pneumococcus antibody solution with a death rate of 21.4 per cent. A control series of 410 cases in the same institution during the same period of time showed a death rate of 28.3 per cent. Pneumococcus antibody solution produced its most striking effect in pneumococcus Type I cases. It has little if any effect on the Type III cases. Conner treated 103 cases of pneumococcus pneumonia with pneumococcus antibody solution, with a death rate of only 10.6 per cent. for the whole series. This series of cases was treated in New York Hospital where the usual death rate for lobar pneumonia is 30 per cent. The beneficial results obtained with antibody solution appear to be due in part to the protective substance which it contains and in part to the thermal reactions which frequently follow the intravenous injection of the solution. These reactions, while sometimes beneficial to the patient, can be rather terrifying and are, therefore, a disadvantage. Huntoon has recently succeeded in eliminating the chill-producing substance from some lots of his antibody solution, but the improved solution has had up to this time only a limited clinical application. Felton has also prepared a purified and concentrated solution of pneumococcus antibodies for the specific treatment of pneumonia. Felton's solution contains some horse protein, but much less than that in the original serum. In experiments on monkeys infected with pneumococcus Type I pneumonia the writer has been able to sterilize the blood regularly with both Huntoon's and Felton's antipneumococcus solutions. Similar but

less striking results have been obtained in Type II infections. This line of investigation is still in progress and is very promising, for it offers a method of providing the patient with protective substances in a highly concentrated and purified form. With a concentrated solution of pneumococcus antibodies, polyvalent in character and entirely devoid of horse proteins or chill-producing substances, it may eventually be possible to maintain the sterility of the blood in all types of pneumococcus pneumonia, and thereby reduce markedly the death rate in this disease. Whatever the serum or serum derivative used, the necessity of early and adequate treatment cannot be too strongly emphasized.

Pneumococcus vaccine has been recommended as a therapeutic measure, but there is very little experimental or clinical evidence in its favor. The immune response to pneumococcus vaccine is comparatively slow. Even when the vaccine is injected intravenously, antibodies do not appear in the blood until a week or ten days later. The striking effect sometimes observed after the intravenous injection of pneumococcus vaccine is probably non-specific in character.

Chemotherapy in various forms has been tried in the treatment of lobar pneumonia. The salts of quinin have been advocated by Solis-Cohen and others. German writers have reported favorably on the therapeutic value of optochin, a quinin derivative. Optochin hydrochlorid sometimes produces symptoms of cinchonism. The optochin base is less dangerous, as it is absorbed slowly from the stomach. The reports of Moore and Chesney from the Rockefeller Institute were not particularly favorable to optochin, and our results in the wards of Bellevue Hospital have not been encouraging.

Prophylaxis.—From the studies made at the Rockefeller Institute it seems quite clear that pneumonia, especially of the severer types, is spread largely through the medium of carriers. Stillman has shown that the specific disease-producing types of pneumococci may be present in the mouth of patients as late as ninety days after recovery. In consideration of these facts a patient with pneumonia should be quarantined as rigidly as a patient with typhoid fever. The patient's dishes should be sterilized and particular care should be taken in the handling of sputum. All linen, handkerchiefs, etc., used by the pneumonia patient should be sterilized by boiling. It is important that doctors and nurses should realize that pneumonia is an infectious and transmissible disease and that they should take every precaution against the spread of the infectious agent.

The surest way of preventing pneumonia would be to eliminate the common cold and other mild respiratory infections. In the studies of pneumonia at Bellevue Hospital approximately one-third of the patients gave a history of preceding cold or cough, and careful questioning would probably have shown a much higher percentage. At the present time, however, there is no thoroughly satisfactory and practical method of preventing colds.

It is quite possible to vaccinate both animals and man against pneumococcus infections. Cecil and Steffen have shown that monkeys can be readily immunized against pneumococcus pneumonia by subcutaneous or intravenous injections of pneumococcus vaccine. Lister was the first to employ pneumococcus vaccine on large groups of men. He demonstrated its value in preventing pneumonia among the native workers in the diamond mines of South Africa. Cecil and Austin vaccinated 12,519 soldiers at Camp Upton against the three types of pneumococcus and brought

about a marked reduction in the incidence of pneumococcus pneumonia among the vaccinated troops. The immunity conferred by pneumococcus vaccine is of comparatively short duration, probably less than one year. It is particularly indicated in the case of individuals who are subject to recurring attacks of pneumonia.

Lobar Pneumonia Caused by Other Species of Bacteria.—While the great majority of lobar pneumonias are caused by some type of pneumococcus, other bacteria may under certain circumstances produce a lobar type of consolidation. The *Friedländer bacillus* produces a classic type of lobar pneumonia characterized by a sticky, viscid exudate and massive consolidation, usually of several lobes. The death rate is high and abscess of the lungs is a frequent complication.

Lobar pneumonia is occasionally seen as a complication of typhoid fever. While in most of these cases some type of pneumococcus can be isolated from the sputum, occasionally the typhoid bacillus itself appears to be responsible for the pulmonary condition.

Streptococcus hemolyticus and *Streptococcus viridans* are sometimes isolated from the lungs in lobar pneumonia, and if no pneumococci are present the natural inference is that the streptococcus is responsible for the infection. It is probable, however, that in some of these cases the pneumococcus has initiated the infection, only to be replaced later by the streptococcus.

The influenza bacillus is frequently isolated from the sputum in lobar pneumonia, but probably never produces *per se* a true lobar consolidation. It is practically always associated with pneumococcus or streptococcus and is apparently a secondary invader.

The tubercle bacillus is capable of producing a lobar type of consolidation. Lobar pneumonia of tuberculous origin may run a course quite similar clinically to that of pneumococcus pneumonia. In the majority of instances, however, the tuberculous cases terminate fatally.

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OTHER PNEUMOCOCCAL INFECTIONS

Pneumococcus septicemia of cryptogenic origin is occasionally encountered, usually in children. It is conceivable that in these cases the pneumococcus enters the body through the lungs without producing a local lesion. It is much more probable, however, that some focus of infection has been overlooked (tonsils, teeth, middle ear, gall-bladder, etc.).

Pneumococcus peritonitis may be secondary to pneumococcal infection in the appendix or gall-bladder, or the infection may gain entrance to the peritoneum through the fallopian tubes. (See chapter on Peritonitis.)

Pneumococcus meningitis is seen most frequently as a complication of pneumonia, but may also occur as a complication of mastoiditis with thrombosis of the lateral sinus.

Almost any part of the body may occasionally be the seat of pneumococcal infection.

Russell L. Cecil.

BRONCHOPNEUMONIA

(*Lobular Pneumonia, Catarrhal Pneumonia, Capillary Bronchitis*)

Definition.—Bronchopneumonia is the most common name given to an inflammation of the lung, which usually begins in the terminal bronchioles and extends to adjacent lobules, few or many of which are involved in the inflammatory process. If fusion of separate areas occurs, the consolidation tends to assume lobar distribution. The disease is essentially secondary in character and accompanies or follows such conditions as infections of the upper respiratory tract of unknown etiology, specific infectious fevers, chronic debilitating diseases, and mechanical or chemical irritation of the

bronchial and parenchymal structure of the lung. The causative agents of bronchopneumonia are the ordinary bacteria of the upper respiratory tract.

Etiology.—Bronchopneumonia, unlike lobar pneumonia, develops as a result of complex and diversified etiological factors. Sex appears to have no specific bearing on morbidity rates in this condition. On the other hand, age bears an important relationship to its frequency, and the periods of highest incidence are the very early years of life up to the tenth year and the decades after fifty. These periods of increased incidence are readily understandable when we consider the fact that bronchopneumonia is principally a secondary disease, and that among the most important predisposing factors are the contagious diseases of childhood and the degenerative phenomena of old age. Occasionally specific epidemic infections, such as influenza, which attack individuals in all age periods determine larger outbreaks of bronchopneumonia, because of some distinctive quality of the causative virus, which injures the lungs and lowers their resistance to secondary infection. The greatest number of cases of bronchopneumonia occur during the winter months, the peak of the curve of incidence usually occurring in late February or March. This is largely because of the fact that bronchopneumonia frequently follows certain primary diseases, such as the common cold, influenza, and measles, which have their period of maximum incidence during cold weather.

Bronchopneumonia has no specific bacterial etiology. Almost any pathogenic micro-organism if it gains access to the smaller bronchi and parenchyma of the lungs can initiate a bronchopneumonia provided the tissue resistance be sufficiently lowered. The common organisms concerned in the production of bronchopneumonia are *Pneumococcus*, *Streptococcus*, *Staphylococcus*, and *Pfeiffer's bacillus*, and in regions where bubonic plague exists, *Bacillus pestis*. These organisms play for the most part the rôle of secondary invaders, and require some previous damage to the lung before they are able to establish themselves in the tissues. *B. pestis* is an exception to this statement and causes primary bronchopneumonia frequently of epidemic character. Staphylococcus and streptococcus not uncommonly cause bronchopneumonia as part of the syndrome of general infection due to these organisms, and occasionally are responsible for local lesions in the lungs when the septic process is in a distant part of the body.

The great majority of instances of bronchopneumonia are secondary to already existing disease. The most important predisposing conditions are: the contagious diseases of childhood, such as measles, whooping-cough, scarlet fever, diphtheria, rickets, diarrhea; the infectious diseases of adult life, the common cold, bronchitis, influenza, typhoid fever, and others less common, and the chronic cardiac, vascular, pulmonary, and renal disease of middle and old age.

Important contributory factors to the development of bronchopneumonia under special conditions are the inhalation of irritating gases, harmful chemical substances in the form of dust, and the aspiration of food or other foreign particles from the mouth and pharynx, accidentally during coma or surgical anesthesia. Bronchopneumonia following anesthesia is partly dependent upon the depressant effect of the anesthetic, and is especially common in those individuals who, at the time of operation, have mild infections of the upper respiratory tract.

Morbid Anatomy.—Bronchopneumonia is an inflammation of the ter-

minal bronchioles and adjoining air vesicles. Part or all of a lobule may be involved. Occasionally the air-cells alone are involved in the inflammatory process. In the majority of instances both lungs are affected, as a rule unequally, and the maximum involvement usually occurs at the bases. The pleural surfaces are, for the most part, smooth and glistening, and present a mottled appearance, dark bluish depressed areas of collapse alternating with areas of a lighter red color. Here and there, when the inflammatory process approaches the surface, are found dulling and roughening of the pleural membranes, due to the deposition of a thin layer of fibrin. The affected portions of the lung are somewhat fuller and firmer than normal and in most instances firm, consolidated areas can be felt throughout the lung tissue. The cut surface of the lung is ordinarily moist with fluid blood and dark red in color due to the general congestion. The actual extent of the bronchopneumonia is indicated by the number and size of the projecting reddish-gray areas, which may be either isolated or in groups or may occur in confluent patches, the whole producing a characteristic mottled appearance. The consolidated areas are made more apparent by drawing the lung tissue from side to side, so that the loss of elasticity becomes distinct. If the section has been cut in the axis of one of the lobules, it may show a racemose or grape-like arrangement, corresponding to small bronchi and their associated groups of air cells. Between the solid areas of lung is found tissue more or less normal in color and air-containing. There are also bluish depressed areas consisting of collapsed air-cells whose bronchus has become plugged with exudate. These collapsed areas may be large and involve a considerable portion of a lobe. Occasionally the opposite result is observed and small areas of emphysema are to be seen due to inspiratory distention of the air vesicles. Commonly several solidified patches coalesce and form large masses of consolidation. The process of coalescence may be so extensive as to affect whole lobes or even a considerable portion of one lung, giving rise to the so-called confluent bronchopneumonia. If the process is the end-result of a general bronchitis, the large tubes are involved in the inflammatory process and their mucous membranes are swollen and congested and the lumen contains more or less mucopurulent exudate. Ordinarily the consolidated areas are polygonal in shape with a darker red center due to peribronchial congestion. In the center of such a patch small grayish-white points are apparent and indicate the position of the bronchioles. Pressure on such solid patches causes the appearance of yellowish mucopurulent drops of exudate which can easily be squeezed from the partially plugged bronchi. The walls of the small bronchioles are congested and the latter contain fluid material made up of serous exudate, cells, and occasionally hemorrhagic products.

Microscopical examination of sections through the consolidated areas shows the bronchioles filled with mucopurulent secretion consisting of swollen desquamated epithelium, leukocytes, bacteria, and granular material. The bronchial walls are swollen and thickened and are infiltrated with polymorphonuclear and mononuclear leukocytes. In certain types of bronchopneumonia, such as that accompanying influenza or following measles, the interstitial inflammation is marked and extends into the peribronchial and interlobular connective tissue. There is always more or less denudation of the bronchial epithelium, the blood-vessels are engorged, and here and there is to be seen an irregular dilatation of the bronchial walls.

The blood-vessels of the alveolar walls are engorged and there is always a considerable degree of cellular infiltration of the walls themselves. The alveolar spaces are filled with exudate containing leukocytes both of the large mononuclear and polymorphonuclear variety, and swollen epithelial cells. There is little or no fibrin network and red blood-cells are not commonly present in any numbers except in certain hemorrhagic types of influenzal bronchopneumonia. During resolution the cellular exudate undergoes fatty degeneration and gradual disintegration. Bacterial stains reveal large masses of the type of organism causing the pneumonia. Abscess formation may occur, especially in the septic pneumonias and in the secondary pneumonia due to *Streptococcus hemolyticus* and *Staphyloccocus aureus*. The abscesses may be miliary in size or at times quite large due to the breaking down of considerable masses of lung tissue. In aspiration pneumonia gangrene of the lung may occur, and is usually associated with the presence of putrefactive anaërobic bacteria. When resolution is slow, connective-tissue organization of the consolidated areas and their included bronchi is common, and is especially associated with infection of the lung with streptococcus.

Bacteriology.—Bronchopneumonia can be caused by a variety of pathogenic micro-organisms. The commonest organisms associated with the disease are *Pneumococcus*, *Streptococcus hemolyticus*, *Pfeiffer's bacillus*, *Staphylococcus*, and in the specific bronchopneumonias *tubercle bacillus* and *B. pestis*. In the gangrenous types there are usually many varieties of micro-organisms, including anaërobic bacilli and frequently spirochetes of different types. Mixed infection is common in bronchopneumonia and frequently two or more of the above-mentioned organisms are concerned in the causation of the pathological process. *Streptococcus hemolyticus* is the most frequent cause of the epidemic type of bronchopneumonia.

Clinical History.—(A) *Primary Bronchopneumonia.*—Primary bronchopneumonia is of two types, the infantile form, which attacks children principally under two years of age, and the epidemic variety, which prevails at irregular intervals and is not limited to any age period. The first type mentioned usually develops in children previously in good health, and is very closely allied, if not identical with, true lobar pneumonia. The clinical manifestations, the bacteriology, and the pathology are the same except that the distribution of the pneumonic process is lobular instead of lobar. The pneumococcus is the usual infecting micro-organism. The infection is of a comparatively mild character, most instances ending in complete recovery without complications. Bronchitis is not a conspicuous feature of the disease. The onset is usually abrupt, frequently with vomiting and convulsions. The temperature is of the high continuous type and the termination, just as in lobar pneumonia in adults, is frequently by crisis, which occurs on or about the seventh day. Leukocytosis of varying degrees is a constant feature.

Physical examination of the chest reveals small areas of dulness scattered throughout one or both lungs. Fusion of these areas not infrequently takes place and the disease then assumes all the characteristics of lobar pneumonia. It is important to distinguish the primary form from secondary bronchopneumonia of childhood, since the prognosis is much more unfavorable in the latter variety. The chief points of differentiation are the more acute course of the primary bronchopneumonia with sudden onset and relatively

short duration, and the absence of such predisposing factors as an antecedent bronchitis or some form of specific fever.

Epidemic primary bronchopneumonia is usually due to infection of the lung with hemolytic streptococcus. Outbreaks occur at periods when the equilibrium of population is disturbed such as generally takes place during great wars. Streptococcus is ordinarily a secondary invader of a previously diseased or injured tissue, but when the ground is favorable achieves great virulence and soon attains the capacity to cause primary inflammation of the lungs. The last large outbreak of streptococcus pneumonia in America was during the Great War. The organism first established itself as a secondary invader in post-measles pneumonia. It quickly achieved independence of this disease and appeared as a primary cause of bronchopneumonia both in the military and civilian population. Epidemic pneumonia of this type is severe in character and very fatal. The leading symptoms are severe intoxication, a high remittent type of fever, cough with mucopurulent or bloody expectoration, intense dyspnea and cyanosis, and a remarkable tendency to early infection of the pleural cavity, with the development of empyema. The effusion is sometimes present within twenty-four hours from the time of onset; is at first blood-stained in character, containing innumerable streptococci; and later becomes frankly purulent. The intrapulmonary process is frequently obscured by the effusion, and the physical signs may not be unlike those of lobar pneumonia, the fluid transmitting the bronchial breathing quite distinctly. The pneumonia is septic in type and not infrequently results in the formation of pulmonary abscesses. Recovery is slow and convalescence long drawn out, especially when the disease is complicated by empyema. The mortality is high at the beginning of the epidemic, but becomes less as it draws to a close.

(B) *Secondary Bronchopneumonia.*—The symptomatology of the secondary type of bronchopneumonia is not of a very specific and typical character. The picture of the disease in children differs from that seen in old age. The onset and clinical course are also modified by the nature of the predisposing condition. The bacterial cause and whether the infection be pure or mixed influence materially the appearance of the disease. Many times the symptoms are trivial and indefinite, so that the existence of pneumonia can only be guessed at from slight changes in temperature, respiration, and general condition. On the other hand, especially in young children, the disease may be fulminant in character, death occurring within two or three days.

The onset is usually gradual, the symptoms of the antecedent disease passing slowly or quickly into those of bronchopneumonia. Sometimes there is a short interval of improvement before acute symptoms reappear. In old people, in whom bronchopneumonia frequently accompanies acute bronchitis, there is no sharp line of demarcation between the bronchitis and the pneumonia, the symptoms becoming progressively more severe. The presence of pneumonia is indicated by an increase of the fever of varying degree, and increase in the rapidity of respiration and pulse, and the more pronounced character of the constitutional disturbance. Cough, if present, becomes more frequent and distressing and the sputum is usually increased in amount. The character of the sputum is variable, sometimes in the beginning frothy mucus, not infrequently blood-stained, or even frankly bloody. Sooner or later, if the individual survives, the sputum be-

comes mucopurulent. In old people and young children the cough is frequently ineffective and the sputum swallowed. Toward the end in fatal cases the cough gradually subsides, the lungs fill with coarse, moist râles, and death takes place from asphyxia and respiratory failure. The pulse rate is constantly increased and, in general, is directly proportional to the severity of the pneumonia. It is especially rapid in infants and old people with chronic disease. In the early stages it may be full and bounding, but if progress is unfavorable quickly becomes weak and thready and at the last may be irregular. Varying degrees of cardiac dilatation are not uncommon, and in the severe and prolonged instances of the disease the heart sounds lose their muscular quality.

The respirations in all but mild cases are rapid and in children may reach or even exceed seventy per minute. In adults the rate is somewhat slower. If the process is severe the dyspnea is often marked and in children there is frequently a pulling in of the soft parts of the chest wall. Cyanosis is an important symptom of bronchopneumonia and varies in intensity with different types of the disease, usually being most pronounced in the influenzal form. It makes its appearance first on the lips and ears and then on the tips of the fingers, the ordinarily pink color of the nails assuming a bluish tinge. In fatal cases the face becomes almost livid and the surface of the whole body cyanotic. Just before death the cyanosis is replaced by a gray pallor, and the skin becomes cold and clammy. Cyanosis is the visible manifestation of variable degrees of anoxemia and depends upon the severity of intoxication and the mechanical interference with the circulation and aëration of the blood in the lungs.

The temperature in bronchopneumonia is generally of the remittent type. If fever exists before the development of the pneumonia the temperature rises with the beginning of the pulmonary involvement. The degree of fever varies between 101° and 104° F. In the grave form in children the temperature may rise as high as 106° F., and in old people with weak reactive power it may never be higher than 101° F. even though the outcome be fatal. The remissions are usually fairly well marked and the lowest point of the curve is reached in the morning. The fever lasts anywhere from five days to a month or more, and there may be relapses if the pneumonic process spreads to other parts of the lungs. An increased temperature lasting more than three or four days in ordinary bronchitis should lead the physician to suspect bronchopneumonia. The pyrexia generally terminates by lysis, but crisis sometimes occurs, especially when the infecting micro-organism is the pneumococcus.

Symptoms referable to the nervous system are common in young children and consist mainly of restlessness, mental excitement, and delirium. Convulsions in the early stages are less common than in lobar pneumonia, and if they occur usually take place toward the end of severe cases. In old people the delirium is of a low muttering type and quickly passes into coma.

Gastro-enteric symptoms are common in infancy and have an important bearing on the course of the disease. They are dependent upon impaired digestion associated with the infection and consist of vomiting and diarrhea, which add much to the danger of the attack. Tympanites is not so frequent or distressing as in lobar pneumonia, but varying degrees of abdominal distention do occur.

The blood may show a moderate anemia in bronchopneumonia, especially in children. When the case is of long duration the anemia may become pronounced. Leukocytosis is a regular feature of the disease, the white cells of the blood ranging from 20,000 to 40,000 per cubic millimeter, the increase being chiefly in the polymorphonuclear cells. In certain types of streptococcus, staphylococcus, and influenzal bronchopneumonia, especially when the intoxication is profound, there may be leukopenia. Blood-cultures are occasionally positive and most commonly show the presence of either pneumococcus or streptococcus. The urine is scanty, high colored, and at the height of the fever contains a trace of albumin.

The physical signs of bronchopneumonia are in the early stages those of a bronchitis involving the smaller tubes. Fine and medium moist râles are to be heard most frequently at the bases just below the angles of the scapulæ. The presence of a persistent localized patch of such râles at these areas is very suggestive of the existence of bronchopneumonia even in the absence of other signs. Impairment of resonance is absent if the areas of consolidation are small, but as larger portions of the lungs become involved dulness on percussion, usually at the bases, becomes marked. Outspoken tubular breathing is uncommon except in the so-called confluent or pseudo-lobar types. The breath sounds may be normal, suppressed, or broncho-vesicular in quality. Localized persistent fine râles are the first and may be the only physical sign of bronchopneumonia.

Diagnosis.—The actual determination of the existence of bronchopneumonia frequently presents difficulties. The clinical picture is usually more or less obscured by the various predisposing factors. As a rule, the increase in the symptoms, heightening of the fever and respiratory rate, with the appearance of localized râles in the lungs, indicate a beginning pneumonia. The distinction between broncho- and lobar pneumonia is usually not difficult. The insidious onset of bronchopneumonia, its secondary character, remittent type of fever, the mixed character of the râles, and the absence of high-pitched tubular breathing form important differential points between it and lobar pneumonia. The different micro-organisms which produce bronchopneumonia alter the character of the disease somewhat and an effort should always be made to determine the bacteriology of each individual case. Tuberculous bronchopneumonia is frequently difficult to distinguish from the more protracted form of ordinary lobular pneumonia. The continued persistence of signs with loss of weight and evening rise in temperature is strongly suggestive of tuberculosis. The diagnosis is made by the finding of tubercle bacilli in the sputum. It is frequently very difficult to determine whether or not bronchopneumonia exists in individuals suffering from passive congestion of the lungs due to such conditions as chronic heart disease. The presence for some time of a remittent fever with variation in intensity of the physical signs over different portions of the lungs indicates the probable existence of pneumonia. *x*-Ray examination of the lungs reveals rather coarse, mottled, uneven areas of density, fading imperceptibly into normal-looking lung tissue.

Prognosis.—Bronchopneumonia is always a serious disease and especially dangerous to life in young infants and in the aged. The prognosis depends upon such a great variety of factors that no general statement can be made. Influential circumstances are the age, surroundings, nutrition and previous condition of the patient, the bacteriological nature of the infection,

and whether or not the disease is primary or secondary. High fever, rapid breathing, marked cyanosis, and rapid heart rate are all bad prognostic signs. Recovery not infrequently takes place in what appears to be almost hopeless cases, especially in children. In adults with chronic debilitating affections the disease is extremely fatal and is the common cause of death in these conditions.

Prophylaxis.—Much can be done prophylactically to prevent the development of bronchopneumonia. In children recovering from the specific fevers a proper period of convalescence in bed should be provided and exposure to cold carefully guarded against. Catarrhal affections of the nose and pharynx must be promptly attended to and the mouth and throat should be washed or irrigated frequently to remove the secretions and promote proper function. Contact with outsiders should be strictly limited and in hospitals every effort made to provide individual isolation. Streptococcus and pneumococcus are passed with great facility from individual to individual and are the cause of the great majority of cases of bronchopneumonia. The aged and those suffering from chronic disease should be especially careful if suffering from the common cold, an important factor predisposing to bronchopneumonia, and whenever possible should be kept in bed during the acute stages of this infection. Sputum should be collected in suitable receptacles and burned, and eating utensils kept separate and sterilized.

Treatment.—There is no specific therapy for bronchopneumonia, except in certain exceptional instances when the infection is due to Type I pneumococcus and the appropriate antipneumococcus serum can be used to advantage. The administration of vaccines during the course of the disease is of doubtful efficacy. In the absence of any specific remedial agent the general management of the case must be adapted to the special needs of the individual, and it sometimes taxes the ingenuity of the physician to the utmost. The accepted therapy is much the same as that for lobar pneumonia. Plenty of fresh air is important, but care must be taken to avoid exposure to undesirable degrees of cold or draft. A moderate temperature is best. The patient should be given as much food as he can assimilate with comfort. It may consist of semisolids or fluids, and includes eggs, custards, toast, milk, and nourishing soups. In young children great care must be taken to avoid disturbing the gastro-intestinal tract by improper feeding or overmedication. In protracted cases the caloric intake should be maintained at the appropriate level if possible. The bowels should be regulated with mild laxatives and enemata. Active purging is not advisable. Water should be given freely. External hydrotherapy is no longer much used in the treatment of pneumonia, though a mustard bath is sometimes of value for children. In old people a sitting posture frequently affords relief if dyspnea is marked and occasional change of position prevents the bronchi from becoming flooded with secretions. Local pain in adults due to pleural inflammation is best treated by the application of hot poultices and the administration of small doses of codein or morphin. The cough is frequently troublesome and, though necessary for the removal of sputum, frequently must be controlled by giving codein 0.016 gm., or paregoric 4 c.c. whenever necessary. The value of expectorant drugs is doubtful. If the bronchitis is marked, relief is sometimes afforded by repeated inhalations of compound tincture of benzoin or oil of pine. Digitalis is of value, especially in adults,

both for its effect on cardiac muscle tone and its controlling influence over the conducting system of the heart should irregularities occur. It should regularly be given to the aged. Oxygen should be given if cyanosis is present and anoxemia marked. The manner of administration is of great importance, since the older methods are valueless. The modern procedures are such as are described in the article on Lobar Pneumonia. Careful nursing and watchfulness on the part of the physician are the secrets of success in the treatment of bronchopneumonia and the relief of embarrassing symptoms is a most important factor in promoting recovery.

A. R. Dochez.

ACUTE TONSILLITIS

Definition.—Acute tonsillitis is an acute streptococcal infection of the faucial tonsils, which, however, involves the other lymphatic structures of the throat as well.

Etiology.—The disease is usually sporadic, but may at times be epidemic. It occurs most frequently in individuals between ten and thirty years of age. Young infants may be attacked, however, and old age does not confer complete immunity. The incidence is highest during the period of inclement weather—spring, fall, and winter. Persons living in unhygienic surroundings are prone to the disease. It often follows in the wake of epidemics of scarlet fever, measles, and diphtheria. Patients seem to inherit a susceptibility to this infection and occasionally it is seen after operations upon the nose and sinuses.

Chronic hypertrophy of the lymphatic structures of the throat seems to increase the susceptibility. As the disease is infectious, one member of the family may readily pass it on to another. The condition is intimately associated with acute rheumatic fever, and Osler quotes Cheadle as describing it as one link in the rheumatic chain. The older authors state that the "rheumatic diathesis" predisposes to acute tonsillitis. Endocarditis, chorea, and acute nephritis are sequelæ. Frequently acute tonsillitis precedes acute articular rheumatism. Cultures show that the disease is chiefly a streptococcus infection, but that occasionally the *Staphylococcus* or *Pneumococcus* are responsible.

Morbid Anatomy.—There is marked swelling and congestion of the tonsil with proliferation of the parenchymatous lymphoid tissue. The epithelium of the crypts becomes eroded in places, and the crypts themselves filled with an exudate which projects beyond their openings and at times collects as a membrane on the surface of the tonsil. The glands of the neck are somewhat enlarged. One or both tonsils may be involved, and occasionally infection of one follows resolution of the other. A similar, less severe process also occurs at times in the other lymphatic structures of the throat, *i. e.*, at the base of the tongue, and in the adenoid and lymphatic follicles on the lateral and posterior pharyngeal walls.

Symptoms.—The onset is usually marked by sensations of chilliness or a definite chill, aching pains in the back and limbs, and a rapid rise of the

temperature to 103° or 104° F. In children the temperature not infrequently reaches 105° F. The throat is sore and has a characteristic appearance, and swallowing soon becomes difficult. The tongue is coated, the entire pharynx dusky red; the tonsils are swollen to perhaps double the normal size, and the yellowish-white exudate may fill the crypts. There is slight enlargement of the cervical glands. Prostration is marked and the usual symptoms of fever are present. In children the pulse is increased and respiration rapid. The urine is scanty, highly colored, and usually loaded with urates; albuminuria is associated only with severe cases. The average *duration* is from three to seven days. Usually the disease leaves the patient weak and prostrated.

Complications.—*Acute rheumatic fever* frequently follows acute tonsillitis. In the virulent epidemic type, *endocarditis, pericarditis, pneumococcic peritonitis,* and *pneumonia* may follow. *Acute otitis media* is not an uncommon complication. *Peritonsillar abscess* frequently ensues. Occasionally *paralysis* resembling that of diphtheria results.

Diagnosis.—At times it is difficult to distinguish acute tonsillitis from *diphtheria.* Typical acute tonsillitis is readily recognized by the swelling of the tonsil, the yellowish-white patches in the follicles, and the redness and congestion of the pharyngeal mucous membrane. In diphtheria the tonsils are not enlarged, the membrane is dusky gray, and not patchy. It clings to the tonsil, leaves a bleeding surface when removed, and may spread to the pharynx and uvula. The exudate in tonsillitis does not spread to the pharynx, and is easily wiped away from the congested tonsillar surface.

In all cases a culture should be taken and examined for the presence or absence of the *diphtheria bacillus.*

Treatment.—There is no specific treatment for acute tonsillitis. It is, therefore, desirable that the patient stay in bed until the temperature is normal, be restricted to a fluid diet, and take large amounts of water to which sodium carbonate may be added. The mouth should be kept clean with an antiseptic gargle (hydrogen peroxid, 4 drams in half a glass of water). After every acute attack the heart should be carefully watched. Tonsillectomy is necessary if the attacks recur frequently.

TRUMAN L. SAUNDERS.

SCARLET FEVER

Definition.—Scarlet fever is an acute infectious disease caused by the *Streptococcus scarlatinæ,* and characterized by a sore throat and a punctate rash on the skin and roof of the mouth, followed by desquamation.

History.—Scarlet fever in early times was confounded with measles and rubella. It was first definitely described by Sydenham in 1675 under the name of "febris scarlatinæ" as a mild, harmless disease. It was undoubtedly observed by Ballonius in a Paris epidemic of 1574, and in 1619 Sennert in Germany accurately described the disease. The severe epidemics of diphtheria in the eighteenth century led to much confusion with scarlet fever, and this, in a measure, was not cleared up until the discovery of the diphtheria bacillus.

Incidence.—*Age.*—Scarlet fever is essentially a disease of early childhood. The susceptibility is particularly great from birth to the eighth

year. The morbidity, as well as the mortality, falls rapidly with increasing age. According to McCollum, the mortality is 33 per cent. in the first year, about 25 per cent. in the second and third years, 15 per cent. in the fourth, 11 per cent. in the fifth, and 7 per cent. in the sixth and seventh. In the eighth year there is a drop to between 3 and 5 per cent., where it remains throughout life. The mortality varies greatly in different epidemics, but, according to statistics from city health departments, has been definitely reduced in the last fifty years.

Race.—The black race is relatively immune to the disease as compared with the white.

Seasonal Incidence.—Epidemics are more common in the fall and winter, and gradually subside in the summer. The relation between school attendance and the numerical distribution of scarlet fever cases during the year is very evident. The incidence rises rapidly with the opening of school, and falls abruptly with its closing in June.

Familial Immunity.—The susceptibility in families seems to vary essentially with age. Sometimes in large families, when no quarantine is possible, only a single member contracts the disease. There is a definite tendency, however, for some families to react violently to the scarlet fever virus, 3 or more children dying in a relatively mild epidemic. Infants with exudative diathesis are particularly subject to a severe form of scarlet fever, especially the anginose type. Certain families seem to be predisposed to the complicating nephritis.

Other Diseases as Predisposing Factors.—*Infections of the throat* seem to predispose to scarlet fever. Schick cites three instances of scarlet fever infection after an attack of diphtheria in physicians who had previously worked in scarlet fever wards without contracting the disease. Further predisposition to the disease seems to be caused by *surgical wounds*, *puerperium*, and *injuries*, particularly burns.

The Portal of Entry.—That the pharynx is usually the portal of entry is evidenced by the primary localization there. In exceptional cases the streptococcus of scarlet fever may enter through an operative wound, a burn, the uterus at childbirth, or an injury received during the postmortem examination of a scarlet fever patient.

Etiology.—For many years numerous investigators have claimed that scarlet fever was a streptococcal infection, and recently Tunnicliff and Dochez have shown a specific immunological reaction for streptococci isolated from the throats of patients with scarlet fever. It remained for Dick and Dick, however, to reproduce the disease experimentally in man with a streptococcus isolated from an individual with scarlet fever. With the filtrate from this organism they were able to produce in susceptible subjects a skin reaction that indicated susceptibility to the disease. They, as well as Dochez, were also able to produce an antitoxin in horses. It thus appears that the causal relationship of the streptococcus to scarlet fever has been definitely proved.

Mode of Infection.—In most cases infection occurs by direct contact. In sharp contrast to measles, the disease is not very contagious during the incubation period. Scarlet fever is rarely transmitted by droplet infection, but may be communicated indirectly, although infrequently, by articles contaminated by the organism. The scarlet fever streptococcus can persist for months, even for years, in garments, books, toys, and other articles,

and is thus more easily transmitted by a third party than are some of the other infectious diseases. It can be conveyed by milk which has become infected in handling. So far as is known, there is no disease in cattle which corresponds to scarlet fever in man.

The *incubation period* is variously estimated to last from one to eleven days; it is occasionally longer, the usual length of time being from two to five days. The more severe the disease, the shorter the incubation period.

The period during which the patient can transmit the disease is indefinite. It is probable that scarlet fever is not communicable during the period of incubation, and that it is only slightly so at the onset of the disease. In the past the period of desquamation has been considered that of infectivity, but it has been shown that children, when still desquamating, can return to their homes without transmitting the disease, although others, in whom desquamation is complete, have conveyed the infection. Probably persistent discharges from the nose, throat, and ears are infective long after desquamation has ceased, and their presence should determine the length of quarantine. In mild cases, when discharges from the upper respiratory tract are absent, an interval of three to four weeks seems to be sufficient to prevent the spread of the infection.

Morbid Anatomy.—The morbid anatomy of scarlet fever is not characteristic. There is an acute dermatitis of varying intensity which is maximal in the hemorrhagic form. Changes in the capillaries of the skin have been observed during life. The lesions in the throat may be catarrhal, membranous, or gangrenous, according to the severity of the infection, and differ in no respect from those produced by other hemolytic streptococci. There is constant hyperplasia of all lymph-nodes, particularly those of the neck. The changes in the internal organs are practically identical with those produced by other streptococcal infections. The typical renal lesions are characterized particularly by infiltration of the cortex with plasma-cells around the glomeruli and the blood-vessels. Diffuse glomerular nephritis is frequently and characteristically associated with scarlet fever during the second and third weeks of the disease.

Symptoms.—The onset of scarlet fever is usually very abrupt. The child may go to school perfectly well, and in the midst of a class become suddenly ill with nausea, fever, and sore throat. Vomiting is one of the most constant early symptoms. When seen soon after onset the patient has a high fever, the skin is dry, and there is a tendency for the cheeks to be reddened, while a peculiar pallor is noticeable around the mouth and nose (circumoral pallor). Usually the weakness, sore throat, and headache make the patient feel sick enough to go to bed. The temperature generally rises very rapidly to between 103° and 105° F. Although the face is flushed, there is no definite *rash* until six to twenty-four hours later, when numerous, fine, red macules appear around the hair follicles, and by confluence produce a deep blush of the skin. The rash usually appears first on the neck behind the ears, and on the chest, gradually spreading within twenty-four hours to the arms and legs. In more severe cases it assumes a more definitely papular form, resembling goose-flesh because of the localization around the hair follicles. When the scarlet fever is still more severe, little vesicles may form on the papules. In well-developed scarlet fever the rash is quite uniformly spread over the entire surface of the body. In the mild cases and sometimes in a severe case it may be patchy and

restricted to the soft folds of the axilla, the elbow, the groin, and inner aspect of the thigh. On the lower extremities small areas of a punctate rash around the hair follicles on the dorsum of the foot are often the only local evidence of a rash. In *malignant scarlet fever* the rash is often hemorrhagic, and can be entirely obliterated by pressure in the early stage; the anemia persists for a certain length of time, the rash returning in pin points around the follicles on a definitely yellowish background (icteric). The skin usually feels hot and dry, and is slightly edematous. Itching is a variable symptom not dependent on the severity of the rash. Since in mild cases the rash may appear in small areas and persist for only a few hours, it is of the utmost importance to examine the entire body repeatedly for its presence.

Quite as characteristic as the rash is the *exanthem* on the soft palate and roof of the mouth, which consists of a fine, punctate eruption and is, perhaps, the most constant sign of scarlet fever. In the early stage the tongue is heavily furred, tending to be red at the tip and sides; the papillæ are definitely enlarged and occasionally show through the thick fur in the center. In the course of a few days the heavy white membrane desquamates, leaving the tongue smooth and red, with numerous large papillæ on its surface—the so-called *raspberry* or *strawberry tongue.*

The *pharyngeal symptoms* are definite, although there may be only slight redness or injection of the fauces, particularly in patients without tonsils. If the tonsils are present, there is generally definite swelling, and in most instances a follicular exudate. When the disease is severe the patches of membrane may coalesce so as to resemble that of diphtheria. If in the first two days of the disease the membrane spreads beyond the tonsils, it is often due to complicating diphtheria. The swelling involves all of the pharyngeal structures. In children in particular the tonsils may meet in the median line.

Secondary to the throat infection there is *swelling of the glands of the neck*, particularly the so-called tonsillar gland at the angle of the jaw. The posterior cervical glands are rarely much enlarged. There is also a general adenopathy, and in most cases the axillary, inguinal, and cubital glands are palpable.

The *temperature* usually reaches its maximum within twenty-four hours, continues high for from three to five days, and then gradually falls by lysis. The height of the fever indicates the severity of the infection, but very severe scarlet fever may prove rapidly fatal when the temperature is low.

The *pulse rate* usually ranges from 120 to 160 and, if there is hyperpyrexia, may be difficult to determine. In the septic cases with marked cyanosis the pulse is very weak and can be felt only with difficulty.

There is generally a very definite *polymorphonuclear leukocytosis*, the white cell count varying from 15,000 to 30,000 or more. The polymorphonuclear cells constitute from 85 to 95 per cent. of the leukocytes. Particularly interesting is the absolute and relative increase in the number of eosinophilic cells after the second day, as many as 5, 10, and 25 per cent. having been reported, although usually only 1 to 2 per cent. are present, even at the height of leukocytosis.

At the onset of the disease there is usually *mild albuminuria* with no further evidence of renal irritation. The *involvement of the nervous system* is generally in proportion to the height of the fever. Young children sometimes have a convulsion at the onset. Delirium may appear after

the second day, and is in a general way associated with the severity of the infection. *Diarrhea* may develop at the onset of severe scarlet fever; when it appears late in the septic type, it may be caused by streptococcal enteritis.

Desquamation is one of the most typical signs of scarlet fever. As a rule, the degree is directly proportional to the severity of the rash. The process begins on the chest and progresses as did the rash. It is usually complete in from two to three weeks on the body, and may continue for from four to seven weeks on the palms of the hands and soles of the feet. When the disease is mild desquamation is later than when it is severe, but usually there is an interval of from three to ten days between the disappearance of the rash and the first indication of desquamation. During this period diagnosis of scarlet fever is sometimes very difficult, and the only indication of the disease may be the breaks in the skin below the nails of the fingers and toes which can be seen when the ball of the finger or toe is pulled away from the nail. This skin peels back rapidly in a few days. In infants desquamation is usually insignificant, and the characteristic massive peeling of the hands and feet may be absent because the skin is thin. A disproportion between the rash and the peeling is also noticeable in septic scarlet fever with cyanosis, in which the rash may appear only in patches and the desquamation be very intense, particularly on the palms of the hands and the soles of the feet. Complete casts of hands and feet have formed in severe cases. The secondary desquamation due to rapid drying of newly formed skin makes it difficult to determine the end of primary desquamation. This process may be repeated a number of times.

Varieties of Scarlet Fever.—Scarlet fever may be present without eruption, fever, angina, or desquamation. Mild scarlet fever is usually very difficult to recognize unless there is an epidemic. There is generally a mild sore throat and a rash which develops only in patches in the folds, and persists for from twelve to twenty-four hours. This is so insignificant that it is easily overlooked if not especially searched for. In mild epidemics a sore throat is often the only manifestation of the disease. The distinction between scarlet fever and a streptococcal sore throat is then very difficult. Sometimes there may be subsequent desquamation, even if careful observation has revealed no rash. Isolation of the specific streptococcus of scarlet fever helps to differentiate these cases. A type of scarlet fever, associated particularly with severe anginose symptoms, may cause no cutaneous manifestations. The difficulty of diagnosing this type is particularly well illustrated by an instance in which 3 brothers had scarlet fever in turn. The first had a typical follicular tonsillitis without rash; a week later the second developed a similar angina with punctate erythematous patches of a very evanescent nature on the chest and in the axilla; and after another week the third boy came down with typical scarlet fever of moderate severity.

The usual form of scarlet fever is characterized by a sudden onset, with vomiting, and a rise of temperature to 103° F. within a few hours, followed by the appearance of a rash on the neck and chest, which covers the entire trunk and extremities during the next two days, and persists for from four to five days before its gradual subsidence. The desquamation, as a rule, begins eight or ten days after onset. The throat usually shows

the typical follicular tonsillitis, with considerable swelling of the fauces; and the typical punctate rash appears on the soft palate and roof of the mouth. The characteristic strawberry tongue and moderate adenopathy are present. The patient is usually very uncomfortable because of the high fever, general malaise, and painful sore throat. Five or six days later, when the fever and sore throat have disappeared, the patient feels ready to get up, a fact which makes the subsequent isolation of about four weeks irksome and frequently very difficult to manage.

Severe scarlet fever can be divided into the *fulminating toxic type* and the *anginose* or *septic type*. In the first the patient is overwhelmed by the infection and dies within twenty-four to forty-eight hours from rapid heart failure without manifesting any very definite signs indicative of the disease. The rash may be merely a blush with a patchy appearance over the trunk and extremities, and none of the characteristic punctate features. There is usually marked cyanosis and the patient is stuporous, generally in a state of constant, increasing delirium. Another toxic type is manifested by high fever, great restlessness, headache, delirium, and an intense scarlet rash which is often hemorrhagic. There may be hyperpyrexia, the temperature rising to 108° or 110° F. Death, as a rule, takes place within from forty-eight to seventy-two hours. The two toxic types are due to the specific scarlet fever toxin and if treated early respond to the antitoxin.

In the *anginose* or *septic form* of scarlet fever the severity of the throat infection is the most striking feature. The exudate from the tonsil becomes confluent and spreads to the other structures of the throat. Instead of clearing up at the end of three or four days, as is customary, the swelling progresses. There is dysphagia and difficulty of respiration, discharge of a profuse serosanguineous material from the nose, and often early involvement of the ears. This condition resembles that of malignant diphtheria, and the process may involve the larynx and trachea. If death does not occur in this acutely septic state, there may be marked sloughing of the throat, with formation of deep abscesses and general sepsis. Often a cuirass-like swelling develops. This type is seen more often in infants and young children.

Sequelæ.—The sequelæ of scarlet fever are so common that they have come to be regarded as merely a second phase of the disease (Pospischill's *Scharlach Zweite Erkrankung*) which usually develops after an interval of from ten to fourteen days. In severe cases the primary phase may persist and merge with the second; in the mild cases the secondary phase may be entirely absent. It is in this second period that the so-called sequelæ—otitis media, sinusitis, adenitis, nephritis, arthritis, and gangrene—occur. At the end of the first week the patient with the usual type of scarlet fever has a normal temperature and is free from symptoms, but not until the fifth week has passed is he safe from the second phase.

Angina, Tonsillitis, Cervical Adenitis, and Cellulitis.—As in the primary infection, there may be very definite angina and tonsillitis, associated with severe pain, dysphagia, and difficulty in speaking. Peritonsillar and retropharyngeal abscesses are not uncommon. Severe sloughing, leading to erosion of vessels and fatal hemorrhage, may take place in the pharynx. Secondary to this flare-up in the throat and often occurring without any definite angina is an enlargement of the cervical glands. In the severe conditions this becomes marked and often leads to the forma-

tion of an abscess. The infection, particularly in young children, may spread beyond the gland, so that the entire neck is indurated. The skin becomes tense and drawn, the head is retracted, and there may be considerable dyspnea caused by pressure on the trachea. If death does not take place during the acute stage, it is likely to result later from hemorrhage caused by ulceration into an artery, or from pyemia produced by loosening of septic thrombi from one of the larger vessels of the neck.

Otitis media, one of the most common complications, results from extension of the streptococcal infection in the throat to the middle ear, and is characterized by rapidity of development. An ear-drum that appears pearly white may, in a few hours, become red and bulging, or be rendered opaque by desquamated epithelium, and perforate in less than twelve hours. The tendency of the streptococcus to destroy the drum membrane is responsible for the deafness which often results from scarlet fever. Even when the drum is incised early the process may extend to the mastoid cells, the lateral sinus, the meninges, or the brain.

Nephritis.—During the height of the acute febrile period there is only slight albuminuria without other evidence of renal irritation. At times very severe throat complications are associated with a focal nephritis characterized by minute abscesses. Typical nephritis develops during the second or third week of the disease, but in exceptional instances may not appear until later. It is found in about 10 per cent. of all patients and in about 50 per cent. of those with membranous angina. The severity of the disease is no indication of the severity of the complicating nephritis; a very severe nephritis may follow mild scarlet fever. Quite constantly preceding or accompanying the nephritis is the recurrent adenitis.

Postscarlatinal nephritis is of three types—the mild, the usual, and the acute. In a large percentage of the *mild cases* with sequelæ affecting the throat and cervical glands the urine will show albumin and a few casts, and at times even a few erythrocytes can be found. There are no clinical signs of renal insufficiency except transient edema. In the *usual cases* the symptoms are puffiness of the eyes, edema of the lower limbs, anorexia, and pallor. The urine may either contain only albumin and casts for a few days and then become hemorrhagic, or may become suddenly dark reddish brown, less abundant, and loaded with albumin, red blood-cells, and casts. This condition may continue for a number of weeks before the nephritis gradually disappears or, exceptionally, may become chronic. At any time during the acute course the kidney may cease to function and signs of uremia appear. In *acute cases* the course is extremely rapid. The first indication of renal insufficiency may be a convulsion. There is constant nausea and vomiting, fever, restlessness, and convulsions. The urinary secretion may cease entirely or the urine may be scanty, bloody, filled with casts and red blood-cells, and coagulate solidly on heating. With proper treatment it is surprising how many children recover from this acute uremia. Certain families seem especially vulnerable to nephritis, but in spite of the fact that it is severe and often long continued, there is a very good outlook for complete recovery. McCollum found that nephritis became chronic in only 20 of 5000 cases.

Arthritis.—There are two types of scarlatinal arthritis: the first, a severe but, fortunately, rare complication, is septic and suppurative, being a manifestation of the generalized streptococcal septicemia which usually

involves the large joints and is likely to be multiple; the second and ordinary form, the so-called scarlatinal synovitis, is very common in some epidemics, usually appearing at the end of ten days in the wrists, hands, elbows, and knees. It is manifested by redness, some pain, and swelling due to synovial distention. As a rule, there is spontaneous recovery in the course of a week.

Cardiac Complications.—Endocarditis, acute articular rheumatism, subcutaneous nodules, and chorea are probably produced by mixed infection rather than by the scarlet fever virus alone. Such cardiac complications which are most common in the severe toxic and septic cases result from marked fatty degeneration of the myocardium. Sudden disappearance of the more or less intense rash usually indicates heart failure. As in other acute diseases, cardiac murmurs are practically always audible in children when the scarlet fever is severe. In the septic form malignant endocarditis may be associated with purulent pericarditis. More frequently simple endocarditis develops which corresponds more closely to the rheumatic endocarditis.

Complications of the Respiratory Tract.—Purulent sinusitis is a frequent complication of septic scarlet fever. Considering the severity of the throat infection it is surprising how seldom bronchopneumonia complicates scarlet fever. The streptococcus of scarlet fever apparently has no tendency to localize in the lung. Empyema is occasionally a complication.

Involvement of the Central Nervous System.—Osler, in discussing a series of 120 cases of infantile hemiplegia, reports that 7 developed during scarlet fever. *Meningitis* results either by direct extension from the ear or the accessory sinuses, or is caused by septic emboli, endocarditis, or thrombosis. In the more toxic conditions *acute mania* may develop. As a postscarlatinal condition *encephalitis* is rare.

Numerous cases of *gangrene* have been reported which involve small areas of the skin, the hands or feet, and occasionally an entire extremity. The process is often fatal.

Paronychia occurs frequently during desquamation. Children and adults, too, constantly pull off the dead epithelium, and many fissures are caused by rapid drying of the new skin. Infection through these may give rise to a generalized *impetigo contagiosa.*

Relapses, Recurrences, and Second Attacks.—As a rule, one attack of scarlet fever gives immunity for life. The fact that so many individuals who are exposed to the disease do not contract it suggests that much scarlet fever is unrecognized. A patient having more than two attacks of so-called scarlet fever is very likely to be suffering from some other disease. McCollum reports 15 relapses in 5000 cases thirty to thirty-five days after the disappearance of the eruption. In this same series he reports 10 cases of recurrence after an interval of a year.

Relationship to Other Diseases.—The relationship of diphtheria to scarlet fever in patients suffering with the latter is unsolved. The mortality of the diphtheria complicating scarlet fever is almost twice as high as that of the usual type. In some hospitals diphtheria antitoxin is administered every three weeks to all children with positive Schick reactions in the scarlet fever wards.

Diagnosis.—Since scarlet fever has been definitely shown to be a streptococcal infection, it is now possible to identify the specific organism by

its toxin production. The diagnosis must usually be made clinically. Abrupt onset, usually with vomiting, rapidly rising temperature, sore throat, evidenced often by a follicular tonsillitis and marked reddening of the entire fauces, the punctate rash on the hard palate, followed in from twelve to twenty-four hours by a finely punctate blush on the neck and chest which spreads gradually over the entire body, with the characteristic strawberry tongue, and subsequent desquamation are so characteristic that it is easy to recognize the normal cases. The difficulties are presented by the very mild and very severe forms. In mild cases the insignificance of the general symptoms, the inconsequential nature of the rash, the fact that it is patchy and seemingly due to local irritation rather than to systemic disturbance makes recognition very difficult. A sore throat, with a definite punctate rash on the roof of the mouth and soft palate associated with the scarlatiniform rash, must be considered evidence of scarlet fever. The localization of the rash in the groins, axillæ, and folds of the elbows may be of diagnostic aid in the mild cases. Just as difficult of interpretation are the overwhelming toxemias without rash. The rash on the roof of the mouth is usually present, although it, too, may be absent. Careful search of the entire body surface may reveal small patches of erythema. Equally difficult to recognize, particularly in younger children, is the septic streptococcal tonsillitis in which no rash is found even on repeated daily examination, but which produces desquamation by the end of the second week.

Of some value in differential diagnosis is the *Leeds-Rumpel phenomenon*, which consists of spontaneous hemorrhage in the fold of the elbow after constriction of the upper arm with a rubber band. This always occurs in scarlet fever. The *Schultz-Charlton phenomenon* is of pathognomonic sigficance: it consists in the complete disappearance of the rash in from four to six hours in an area about the size of a dollar when the serum of an individual who has recovered from scarlet fever is injected intracutaneously. Dick has shown that this always takes place when the serum is taken from an individual immune to scarlet fever, even when there has been no previous attack.

Differential Diagnosis.—*Dermatitis Exfoliativa.*—The differentiation of scarlet fever from dermatitis exfoliativa (scarlatiniforme) is difficult, for this disease simulates very accurately the anginose as well as the cutaneous manifestations of scarlet fever. Its onset is sudden and accompanied by fever and sore throat. Desquamation of the tongue occurs, and an eruption, which is indistinguishable from that of scarlet fever, develops and is followed by similar desquamation. A primary attack of this disease is practically always mistaken for scarlet fever. Its recurrent nature is the distinguishing feature. Third or fourth attacks of "scarlet fever" are usually dermatitis scarlatiniforme.

Measles.—It is rarely difficult to distinguish measles from scarlet fever. The simultaneous presence of both in the same individual is sometimes difficult to recognize. Measles is characterized by a long period of incubation, the definite prodromal symptoms, the location as well as the character of the rash, and the presence of characteristic Koplik's spots. The typical leukopenia of measles is another differential point. After the disappearance of the rash, patchy pigmentation and branny desquamation indicate measles rather than scarlet fever. At the onset of measles there is occasionally a scarlet-like rash on the chest which precedes by some hours the

typical eruption on the face, the so-called pre-eruptive rash of measles, which may be difficult to distinguish from that of scarlet fever.

Rubella.—Differentiation of mild scarlet fever and moderately severe rubella is often difficult. The rash of rubella may resemble in every way the fine punctate rash of scarlet fever. Its distribution is characteristic, however, since in rubella it is usually on the face, where it is absent in scarlet fever. The angina is usually less severe, but the swelling of the posterior cervical glands more marked.

The rash of *erythema infectiosum* may resemble very closely that of scarlet fever. The characteristic appearance of the rash just after the fall of temperature distinguishes it very definitely from that of scarlet fever. Desquamation is usually slight.

Tonsillitis.—The differentiation of severe follicular tonsillitis with marked systemic reaction, particularly in young children, is practically impossible. In such cases vomiting occurs frequently at the onset. The recent work of Dick and Dick may make bacteriological or immunological differentiation possible.

Smallpox; Chickenpox.—In smallpox and chickenpox there may be a prodromal rash which resembles in no slight degree that of scarlet fever. The absence of marked throat symptoms, the punctate rash on the roof of the soft palate, and the rapid appearance of the typical vesicular lesions usually render diagnosis clear.

Diphtheria.—The difficulty in distinguishing diphtheria from scarlet fever depends largely upon the type of membrane in the throat. Although the two diseases may coexist and develop at the same time, as a rule diphtheria occurs late in the course of scarlet fever. The character of the membrane and its extent may help identification, but only the demonstration of the Klebs-Löffler bacillus can establish diagnosis. A membranous angina occurring late in scarlet fever is usually diphtheritic.

Rash Due to Drugs.—The rash produced by *quinin* in certain susceptible individuals may be punctate in character, resembling scarlet fever not only in itself, but in the ensuing desquamation The absence of any throat symptoms and the taking of the drug are the differential features. *Atropin*, similarly, may cause an eruption very comparable to that of scarlet fever. The dilated pupils, dryness of the mouth, peculiar patchy blush of the face, and absence of any throat symptoms other than the dryness usually differentiate the two conditions. *Aspirin* may produce an erythematic rash with the circumoral pallor. The *iodids, iodoform, luminal,* and *copaïba* may also produce a confusing rash.

Anaphylactic Rashes.—Most typical of the anaphylactic rashes is the *serum erythema* which appears a week or ten days after the injection of serum. The rash may be morbilliform, but is often typically scarlatinal in appearance and distribution. It usually spreads over the entire body very much more rapidly than does the rash typical of scarlet fever. The *ingestion of certain foods* (shell-fish, strawberries, etc.) may give rise to a rash indistinguishable from that of scarlet fever. Knowledge of this idiosyncrasy, together with complete absence of throat symptoms, usually establishes the diagnosis.

In infancy and childhood the *erythemas caused by febrile disease*, especially throat infections, by *strenuous crying*, by *irritating compresses, bandages,* or *ointments,* or *by heat,* may produce a skin picture more or

less closely resembling that of scarlet fever. The absence of other symptoms and a local cause for the rash usually make the differentiation easy.

Prognosis.—The prognosis in scarlet fever is very uncertain. The mortality in different epidemics varies from 3 to 40 and even 90 per cent. The mildest scarlet fever may, in the second or third week, become extremely severe because of the throat and renal complications. The age of the patient is the most important consideration in the prognosis; 33 per cent. of the deaths from scarlet fever occur in patients under one year of age; in the second and third years the death rate is 25 per cent.; it thereafter decreases until the eighth year, when the average adult level is reached. The general conditions of hygiene seem definitely to influence the mortality. McCollum's figures show for Boston, over a period of twenty years, a mortality varying from 1 to 6 per cent. The mortality from 1885 to 1894 was 2.99 per cent., as compared with 1.91 per cent. in the next ten years. Hospitalization of scarlet fever patients in large cities has markedly reduced the number of deaths.

The prognosis in the toxic type is usually grave, but is much better if antitoxin is administered early. Hyperpyrexia, cyanosis, coolness of the skin with patchy erythema, marked early swelling of the lymph-glands, and the tendency to bleeding from the throat and into the skin are of very serious import, especially when they occur early in the disease. The second period of danger is during the second phase of the disease. The prognosis for children who develop nephritis, even if they have had convulsions, is relatively good with proper treatment.

Prophylaxis.—Immediate isolation of every scarlet fever patient, either at home or in a contagious hospital, is essential. If the patient remains at home, individuals not directly exposed may be allowed their liberty if they show no symptoms at the end of eleven days. The danger of carrying scarlet fever is such that the physician should always wear a gown, roll the sleeves to the elbow during physical examinations, and thoroughly scrub his hands after leaving the patient.

When the patient has recovered, everything that can be washed should be thoroughly cleaned with soap and water. Books and playthings must be burned. Bedclothing should be boiled or fumigated in a confined space.

Specific Prophylaxis.—Susceptible individuals, those manifesting a positive Dick reaction, may be actively immunized by the subcutaneous injection of scarlet fever streptococcus toxin. The degree and duration of the immunity has not been satisfactorily ascertained as yet, but seems to last at least one year. Active immunization is especially valuable in checking local outbreaks of scarlet fever in schools, small communities, etc., and for the protection of those intimately exposed to the disease for limited periods of time. Passive immunization may be carried out in special instances by the administration of prophylactic doses of scarlatinal streptococcus antitoxin. The general use of the antitoxin for prophylactic purposes is, however, not advisable because of the relatively short duration of the protection, the low communicability of scarlet fever (only 9 out of every 100 exposed individuals contract the disease), and the severity of the serum intoxication which sometimes follows its use. Children, or others, exposed to scarlet fever should be watched closely for sore throat or other symptoms of the disease, and the temperature should be taken twice daily.

At the first appearance of signs of infection a full therapeutic dose of antitoxin should be administered.

Treatment.—If rigid quarantine cannot be enforced at home, patients should be sent to an isolation hospital. Since in the early stages scarlet fever is not very contagious, immediate isolation protects other members of the household. In the home adequate isolation is practically impossible unless both patient and nurse can be quarantined in a room with adjoining bath. The nurse should have special instruction in the care of infectious diseases and in aseptic technic. Carpets, rugs, and hangings should be removed, and all unnecessary articles taken from the room. Scarlet fever is a self-limited disease, so that in the mild cases general therapy alone is necessary. The patient should be made as comfortable as possible and kept in bed for three weeks. The bowels should be kept open and plenty of fluids, consisting of fruit juices and water, given in addition to the ordinary soft diet. The relation of diet to the nephritis has been widely discussed, and many physicians restrict the food intake to milk during the first three weeks. Pospischill, who studied the effect of diet in a large series of carefully controlled cases, was unable to determine that the incidence of nephritis was higher when a full diet was given than when milk only was allowed.

As soon as desquamation starts the patient should be anointed each day with liquid vaselin and bathed every second day with soap. If there is much itching, carbolic acid (0.25 to 0.5 per cent.) or menthol may be added to the vaselin. At the end of three weeks, if the temperature has remained normal and no complications have developed, the patient may be allowed to get up one hour each day. This period may be increased one hour a day thereafter. Exposure to cold and infection should be carefully avoided for several weeks.

The urine should be examined daily during the first month and carefully examined once a week for at least two months after the illness, because occasionally renal complications develop after an interval of several months. At the end of four weeks, if desquamation is complete and there are no discharges from nose, mouth, or ears, the quarantine may be terminated. The so-called *return cases* are probably due to persisting infection in the nose and ears rather than to infection from scales.

Specific Treatment.—Numerous attempts have been made to develop a curative serum for scarlet fever by the immunization of horses to hemolytic streptococci isolated from patients suffering from this disease. The most effective serum of this type was that produced by Moser in 1902. Moser's serum had a markedly beneficial action on the toxic symptoms of the disease, but fell into disfavor in most countries except Russia because of its low potency, and the severe serum disease that it caused. Convalescent scarlatinal serum has been widely used, and has yielded definitely beneficial results. Sixty c.c. of convalescent serum is given intramuscularly, and the dose is repeated in twenty-four hours if necessary. The results are, however, disappointing in many instances because of the low antitoxin content of such serum, and the variability in the therapeutic effect. The recent work of Dochez and Sherman and of Dick and Dick indicates that a specific antitoxin for scarlet fever can be produced by the immunization of the horse to the streptococcus of scarlet fever and its toxic products. Blake, Trask, and Lynch have shown that such an antitoxin gives a positive Schultz-

Charlton test in active cases of scarlet fever, and neutralizes the toxin which circulates in the blood and is responsible for the toxic manifestations of the disease. Scarlatinal antitoxin, when given in adequate doses in the acute toxic phase of scarlet fever, causes a prompt abatement of the toxic symptoms and disappearance of the rash usually within from twenty-four to thirty-six hours. There is also a sharp drop in temperature and pulse rate, and a diminution of the leukocyte count. In addition, it seems to lessen the number of septic complications and to diminish their severity when used during the acute toxic phase of the disease. It appears, however, to have no beneficial effect on postscarlatinal sepsis after the rash has faded. The dose varies from 3000 to 12,000 units (one unit is the amount of antitoxin necessary to neutralize one hundred human skin test doses), depending upon the size of the patient and the severity of the disease. The antitoxin is usually given

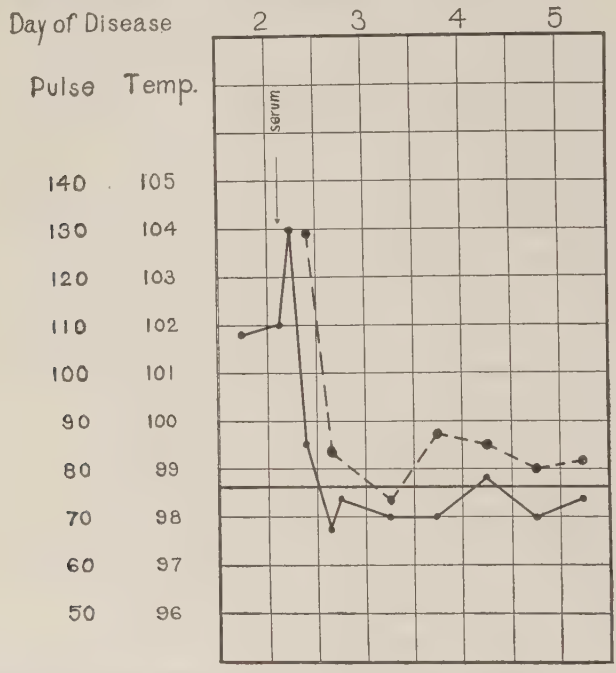

Fig. 2.—Scarlet fever treated with serum on second day of disease. Immediate drop of temperature to normal. Pulse curve is made of a series of dashes.

intramuscularly, but may be used intravenously in case of necessity. Early administration of the serum is essential for satisfactory results.

Symptomatic Treatment.—For the almost constantly present cervical adenopathy the ice-bag is used. It is well to apply this early and not to wait until the glands are swollen. The proper fitting of the ice-bag, particularly in children, is essential. Cold compresses, which can be used in the same way, should be tied over the head rather than around the neck so as to reach the inflamed glands successfully. They ought to be changed every two hours during the day and once during the night. In the later stages, particularly if cold is not well tolerated, heat (a rolled up woolen cloth wrung out of hot water) applied in the same manner often relieves pain, and causes rapid disappearance of the glandular swelling.

If the glands have begun to break down, large, hot compresses should be used and renewed every fifteen minutes for alternate hours. Bullowa has shown that tonsils, so placed that the act of swallowing tends to milk their contents into the lymph channels, should be removed, even in the acute stage of scarlet fever.

It is desirable for older children and adults to gargle with a mild antiseptic solution every three or four hours. For smaller children, or when gargling is painful, irrigation of the throat with warm normal saline, boric acid, or dilute antiseptic solution (several quarts) gives very apparent relief. Such treatment is desirable in the moderate as well as in the most severe septic cases. Application of strong antiseptic solution is contraindicated. The nose should be kept clean, and in case of crusting 0.25 to 0.5 of a 1 per cent. preparation of menthol in liquid albolene inserted several times a day. Cultures should be taken from the throat so as to exclude the possibility of diphtheritic infection, and permit immediate administration of antitoxin if they are positive. The ears must be examined daily, even when there is no complaint. As soon as there is an injection of the drum, 7 per cent. carbolated glycerin should be instilled into the ear, filling the entire canal, and a small ball of cotton saturated with the solution inserted in the canal as a plug. As soon as there is bulging the drum should be widely incised. If the discharge be serosanguineous, no irrigation is necessary; if purulent, the ear should be washed with sterile salt solution or boric acid three times a day. In young children tenderness and edema develop above the ear (subperiosteal abscess) instead of over the mastoid process. The mastoiditis complicating scarlet fever should receive early operative treatment.

For the toxic conditions with marked cyanosis, caffein in frequently repeated doses or camphorated oil given hypodermically is of some value.

The mild nephritis usually needs no special treatment. The patient should be kept in bed on a salt-free diet. The indication for immediate treatment is the rapid development of uremia. Removal of blood (250 c.c. in five-year-old children, 300 c.c. in ten-year-old children, and 500 c.c. in adults) followed by an equal injection of salt solution usually brings the patient out of a state of coma and relieves the convulsions. It may be necessary to repeat such treatment.

Henry F. Helmholz.

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ERYSIPELAS

Definition.—Erysipelas is an acute inflammation of the skin or, rarely, of the mucous membranes, caused by the *Streptococcus hemolyticus*, and accompanied by fever and constitutional symptoms.

History.—The disease was well known to the ancients. Its contagious character was first recognized by Wells in England in 1800, and later by Trousseau. Fehleisen in 1882 demonstrated the streptococcus in the skin, and reproduced the disease in animals by the inoculation of pure cultures.

Incidence.—Erysipelas is a fairly common disease, encountered in every part of the world, but more frequently in temperate climates. Season is not without influence, more cases occurring in the colder months, especially in April. Epidemics were not uncommon in the pre-aseptic era, and still occur occasionally. The disease is sometimes endemic in unhygienic institutions. Individuals of all ages are affected, the greatest incidence being in the third decade of life. Erysipelas is more common in women than in men.

Etiology.—Infection always takes place at the site of a wound, fissure or abrasion, which is often too small to be visible to the naked eye. It may be due to the introduction of organisms from external sources, or to self-infection, as in chronic rhinitis and operations on infected areas (mastoiditis). A predisposing cause is lowering of the resistance for any reason. Persons who have recently undergone a surgical operation and women after parturition are particularly susceptible, also patients with chronic alcoholism or debilitating diseases (chronic nephritis, cancer, etc.). In former times the disease was frequently transmitted from one patient to another by attendants, dirty instruments, or infected dressings. Since the advent of asepsis this has largely stopped, and the source of infection is usually obscure.

Bacteriology.—The causative organism belongs to the group of hemolytic streptococci and almost certainly constitutes a specific strain, as indicated by the experimental work of Tunnicliff (1920) and Birkhaug (1925). Very rarely the staphylococcus has been reported to be the cause. Infection takes place by inoculation of a wound of the skin or mucous membrane.

Morbid Anatomy.—The distribution of the streptococci in the skin is peculiar, for they are found exclusively in the lymphatic vessels, in greatest numbers at the margin of the inflamed area; they are absent in the central portion, where involution is taking place, and are seldom to be found in the contents of the blebs. The histological changes are unusual, in that great numbers of mononuclear cells are present in the corium. Suppuration takes place if the disease extends to the subcutaneous tissues. The viscera undergo the changes common to acute infections, *i. e.*, cloudy swelling and acute splenic tumor. Terminal pneumonia and septicemia, with or without endocarditis, are not uncommon in fatal cases. The symptoms are the result of local inflammation and toxemia.

Symptoms.—After a short incubation period of one to three days the disease sets in abruptly, often with a chill. At the same time, or shortly before or after, the local symptoms appear. Occasionally the inflammation of the skin is preceded by intense soreness and redness of the throat, which may be referable to initial erysipelas of the mucous membrane. *Fever* is almost invariably present and is often high; it is usually remittent

in type, often continuous, rarely intermittent. There are symptoms of toxemia, *i. e.*, malaise, headache, anorexia, and often nocturnal delirium. Vomiting is frequent at the onset.

The most common starting-place of the inflammation is the face, especially about the nose or eyes, less often the ears; this may be accounted for by the frequency of latent streptococcus infections of the nose and sinuses. Other points of origin are the umbilical wound in the newborn, chronic ulcers of the leg, surgical wounds and injuries, and the vulva during the puerperium.

Wherever it may start, the local appearances are much the same. A small area of the skin becomes red and swollen and is tender on pressure. The process spreads rapidly, the margins being sharply marked, elevated, and indurated on palpation, constituting the characteristic "wall." In areas where the skin is very loose no wall is formed. Small vesicles or larger blebs frequently develop. Small, red, tongue-shaped projections may be seen at the periphery, marking the advance of the disease in the lymphatics. Extension is always by continuity; when this is apparently not the case, careful inspection shows that the two inflamed areas are joined by reddened lymphatics. Rarely two or more widely separated rashes are seen, the result of multiple inoculation. Involution takes place after a few days in the parts first involved, while the process is still spreading at the periphery; the skin becomes paler and less swollen, the blebs dry up into crusts, and finally there is a profuse flaky desquamation. The regional lymph-nodes are enlarged, but are difficult to palpate on account of the swelling of the overlying skin.

In *facial erysipelas* the lesion spreads rapidly on the cheek and over the bridge of the nose to the opposite side, giving the familiar "butterfly" appearance. The features are greatly distorted, the eyelids so swollen that the eyes cannot be opened, the conjunctivæ intensely reddened, the skin of the face and ears swollen, red, tense and shiny, and covered with vesicles or blebs. On the forehead the process usually stops at the hair line; in about 12 per cent. of facial cases, however, it involves the scalp, and does not stop until the nape of the neck is reached. These natural stopping places of erysipelas are at the barriers where the skin is tightly bound down to the underlying structures. For this reason erysipelas never passes down over the chin on to the front of the neck. Occasionally it does not stop at the nape of the neck, but extends to the back; it is then likely to extend over wide areas, and even over the entire body.

Recrudescences and *relapses* are not uncommon, and are ushered in by a return or increase of the fever. Examination shows a lighting up of the inflammation at the last stopping place; rarely, the parts first affected may be involved a second time.

Usually the disease lasts between four and eight days, but it may persist for several weeks or more if relapses occur, or if it is of the migrating variety. Termination by crisis is common.

The *blood* shows a polynuclear leukocytosis. Blood-cultures are negative if there is no complicating septicemia. The *urine* shows a febrile albuminuria and often contains urobilin. The spleen is seldom palpable.

Erysipelas is one of those diseases with a marked tendency to recurrence; as many as 20 per cent. of patients have two or more attacks. In rare cases the disease recurs with great frequency, especially at the time

of menstruation. After repeated attacks the skin becomes markedly thickened, as in elephantiasis, and may remain in this condition permanently.

Erysipelas of the mucous membranes is much less common. It occurs chiefly in the pharynx and fauces, sometimes in the nose, and is characterized by an intense, diffuse redness and swelling, with much pain. Very rarely it occurs in the larynx and may lead to stenosis and death by suffocation. The lesion may spread to the skin of the face, but extension in the opposite direction, *i. e.*, from the skin to the mucous membranes, is rare. Occasionally the vulva is the primary seat of erysipelas during the puerperium, and extension often takes place to the adjacent skin, more rarely to the endometrium; in the latter case a fatal septicemia usually results.

Complications.—The commonest complication is the formation of *subcutaneous abscesses* situated at the site of the erysipelatous process. The eyelids are most often affected, the legs next. *Gangrene of the skin* is a rare sequel. *Orbital abscesses* sometimes develop, and rarely may cause optic atrophy and blindness; further extension may occur, and lead to thrombosis of the cavernous sinus, meningitis, or cerebral abscess. *Suppuration* may take place in the frontal sinus or antrum, and rarely in the inflamed lymph-nodes. *Endocarditis* and *arthritis* are occasionally encountered, usually in association with septicemia. *Pericarditis* and *pleuritis* are rare events. Terminal *pneumonia* is not uncommon in the fatal cases; it is usually due to the *pneumococcus*, sometimes to the *streptococcus*. *Acute nephritis* occurs in less than 1 per cent. of the cases. *Phlebitis* is an occasional complication in erysipelas, as in most other acute infectious diseases. *Septicemia* is unusual except in debilitated subjects, and is very fatal, accounting for a large proportion of the deaths. *Diarrhea* sometimes occurs, and may be due to acute enteritis, with or without ulceration.

Pre-existing chronic disease is sometimes favorably influenced by erysipelas. Occasionally malignant tumors undergo a marked recession, or lupus of the skin and varicose ulcers may heal after an attack; and in leukemia the white count may drop temporarily to normal.

Diagnosis.—The diagnosis can usually be made at a glance. The presence of fever and constitutional symptoms is important. From *simple erythema* erysipelas is distinguished by the swelling and tenderness of the skin, with pitting on pressure. *Acute eczema* may lead to confusion, but in this condition fever is absent, the skin is more indurated and less tender, and the "wall" is lacking. In *acute phlegmonous inflammations* the skin feels harder and the margins are not sharply outlined. Erysipelas of the mucous membranes can seldom be diagnosed with certainty unless the skin becomes involved.

Prognosis.—The mortality in hospitals ranges from 4 to 9 per cent. In young healthy adults it is lower, about 1 per cent. In old people and infants, and in those debilitated by chronic disease or alcoholism, the death rate is much higher. When the blood-culture is positive the patient usually dies.

Prophylaxis.—The patient should be isolated. Surgeons and obstetricians should not attend cases of erysipelas. Recurrences may be prevented by treatment of the eczema, chronic sinusitis, etc., which are the usual sources of reinfection.

Treatment.—A large number of local remedies has been advocated, and, as is usual in such cases, none is of proved value. Statistics have shown that the average duration is the same whatever the method of treatment.

Recently good results have been reported by Birkhaug (1926) following the use of a monovalent antistreptococcus serum prepared from the *Streptococcus erysipelatis* after the method of Dochez. The number of patients treated (60) is too small to be convincing, and further observation of a large series of cases is necessary before the value of this serum can be considered proved.

Vaccines and *internal remedies* are without curative value. Attempts to stop the extension of the disease by the use of *contractile collodion* (applied 2 inches outside the advancing margin), or by *injections of antiseptics* into the skin, are usually unsuccessful. The frequent use of cold or hot *compresses* alleviates the pain, and is as efficacious as the popular *ichthyol ointment* (25 per cent.), or the application of saturated solutions of *boric acid* or *magnesium sulphate*. If the eyelids are involved, boric acid solution or argyrol (10 per cent.) should be dropped into the eyes several times a day.

The patient should be kept in bed until the temperature has been normal for several days. The food should be nutritious and easily digestible. Liquids should be given freely—about 3000 c.c. daily. Hydrotherapy, in the shape of the cold pack or sponging with tepid water or alcohol, is useful to control high fever, insomnia, and delirium. Symptomatic medication may be necessary; aspirin or acetphenetidin for the headache, barbital for insomnia, and morphin for delirium.

Surgical measures become necessary if abscesses form.

Wilder Tileston.

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SEPTICEMIA

Definition.—Septicemia is a febrile condition in which bacteria are constantly present in the blood and produce symptoms. It is to be distinguished from bacteriemia, or the temporary presence of bacteria in the

blood without constitutional disturbance. Since septicemia is due to a variety of organisms it is really a symptom-complex rather than a specific disease. In some of the infectious diseases, such as typhoid fever, pneumonia, anthrax, Malta fever, and plague, the causative organism is more or less constantly present in the blood, but these conditions will not be discussed here. In a number of local infections (gonococcal arthritis and perinephritic abscess) the bacteria are carried to their destination by the blood-stream, but since the blood merely acts as a carrier and quickly becomes free from bacteria, these conditions are not classified as septicemia.

History.—As a complication of infected wounds, the condition was known to the ancients, and was described by Hippocrates. John Hunter in 1774 demonstrated the part played by suppurative phlebitis, and Virchow (1856) gave a masterly description of the disease, tracing the source of the metastatic abscesses to infected emboli. Pasteur was the first to prove the bacterial origin of puerperal septicemia, while Oliver Wendell Holmes and Semmelweis had previously in clinical studies demonstrated its infectious nature. Leube in 1878 first described "cryptogenetic" septicemia, or that form which occurs without obvious local infection.

Classification.—Septicemia is "*primary*" when it occurs as an independent process, and "*secondary*" when it is a complication of one of the infectious diseases, such as scarlet fever or diphtheria. It is further classified according to its clinical features, but perhaps the most satisfactory classification is that based on the character of the infecting organism.

The term "*pyemia*" is used to indicate the type in which metastatic abscesses form, but since such abscesses represent merely a complication of septicemia, and are often impossible to detect during life, it is better to discard this term, and to speak of "septicemia with metastatic abscesses."

Etiology.—Septicemia is a fairly common disease in individuals of all ages. Predisposing causes are exposure to cold and wet, fatigue, loss of sleep, chronic diseases, and other agents which lower the resistance to infection. The virulence and number of the infecting bacteria are also of importance in determining whether or not an infection is to remain localized.

Terminal Infections.—A large number of patients with chronic disease die as the result of septicemia. Flexner found in autopsies on subjects with chronic disease of the heart and kidneys that terminal infection (exclusive of tuberculosis) caused death in 84 per cent. The infection was most often local (bronchopneumonia, pleurisy, endocarditis, etc.), but in 20 per cent. there was septicemia. The same rules apply to other chronic diseases, such as cancer, cirrhosis of the liver, and Hodgkin's disease. According to Flexner and others, the explanation of the severity of the infection is probably to be found in a diminution of the number of immune bodies in the blood. The clinical course of terminal septicemia is very rapid; frequently the only symptoms are fever, apathy, and stupor.

Portal of Entry.—The infection may start at any place where inflammatory processes occur. The most common location is the skin, where infected wounds, phlegmons, paronychiæ, boils, carbuncles and bed-sores, or occasionally even superficial lesions, such as a blister from an ill-fitting shoe, initiate the trouble. Next in frequency come puerperal infections and infected abortions, and lastly, localized inflammations of other parts. The tonsils are the portal of entry in septicemia secondary to scarlet fever, diphtheria, and septic sore throat, and rarely in acute follicular tonsillitis.

The infection may start from other foci in the upper respiratory tract, such as mastoiditis (usually by way of sinus thrombosis), infected teeth, or inflammation of the nasal sinuses. The lungs (chiefly in lobar pneumonia), the intestines, and biliary tract are occasionally starting points; appendicitis may lead to abscess of the liver by causing septic thrombosis of the appendiceal vein, but the infection usually stops there, and seldom extends to the general circulation. The genito-urinary tract sometimes is the path of entry, especially after rough or dirty instrumentation. In young persons osteomyelitis is a fairly common cause of septicemia.

Staphylococcus infections usually come from the skin. The *streptococcus* invades either through the skin or mucous membranes, and is the chief cause of puerperal septicemia. The *colon bacillus* comes from the intestinal or urinary tract, the *pneumococcus* chiefly from the lungs, the *gonococcus* from the genito-urinary tract, and the *meningococcus* from the nasopharynx.

Bacteriology.—The *streptococcus* is by far the most common organism, and the *staphylococcus, pneumococcus,* and *colon bacillus* are next in order; less frequently the *gonococcus, meningococcus, bacillus of anthrax, gas bacillus,* and *Bacillus pyocyaneus.* The anaërobic *Streptococcus putridus* has been found in the blood in cases of septic abortion. Septicemia is rarely due to diphtheria or influenza bacilli, to the *Bacillus proteus,* the *Bacillus fecalis alkaligenes,* or the *Micrococcus tetragenus.*

Pathogenesis.—The blood is able to clear itself of small numbers of bacteria by depositing them in the liver and spleen, where they are destroyed. It is probable that this frequently takes place without the occurrence of serious illness. Only repeated infection of the blood or introduction of large numbers of organisms leads to septicemia. Two paths of infection are common, by way of the veins or the lymphatics. Often a thrombophlebitis takes place at the primary focus, and is followed by purulent softening and the discharge of infected emboli into the circulation. This results in the formation of metastatic abscesses, first in the lungs, later in parts supplied by the greater circulation.

Morbid Anatomy.—The spleen is always enlarged, and may be very soft, like dregs of paint, or firm, with enlargement of the follicles. The other viscera undergo cloudy swelling and fatty changes. Small hemorrhages (petechiæ) are frequent, especially in the skin, pericardium, and pleura. The histological lesions consist mainly in cloudy swelling and fatty infiltration; the liver may show foci of necrosis. While true hemorrhagic nephritis is rare, it is not uncommon to find swelling and proliferation of the cells lining the glomerular tufts, and edema and infiltration with large mononuclear cells in the interstitial tissues. The petechiæ usually contain bacteria and are, as a rule, the result of alterations in the capillary walls rather than of emboli. Acute endocarditis develops frequently in septicemia, and is to be considered a complication. It occurs in about 50 per cent. of staphylococcic and pneumococcic infections, and in 8 per cent. of those due to the streptococcus. The mitral is the valve most often involved. Embolism is common—small arteries are obstructed by fragments of blood-clot, vegetations detached from diseased heart valves, or masses of bacteria. The resulting infarcts usually form abscesses. The location of the infarcts depends upon the situation from which the emboli were derived. If they come from the veins, the lungs are primarily in-

volved, though minute emboli may pass through the pulmonary capillaries into the general circulation. If from diseased valves, since the left side of the heart is usually involved, the emboli lodge in the spleen, kidneys, or brain, less often in the skin, subcutaneous tissues, muscles, myocardium, bones, or intestines. The frequency of metastasis varies with different bacteria, being 95 per cent. in staphylococcic, 35 per cent. in streptococcic, and less than 25 per cent. in pneumococcic septicemias. Of the serous cavities, the joints are frequently involved, less often the pericardium, meninges, pleura, and peritoneum.

Morbid Physiology.—The response to infection is similar to that in the acute infectious diseases in general, except that since the bacteria usually gain the upper hand, the production of immune bodies may be assumed to be insufficient. The symptoms are partly the result of the toxemia (fever, headache, prostration, anorexia, pains in the back and limbs) and partly the result of the lodgment of emboli in various parts of the body. Certain bacteria, especially the streptococcus, produce powerful hemolysins which by destroying the red cells may lead to a pronounced anemia. The presence of bacteria in the circulating blood *per se* does not cause any special symptoms.

Symptoms.—The course of septicemia is variable. Four types may be distinguished: the fulminating, which ends fatally within a few days; the acute, which may last as long as four weeks; and the subacute and chronic, which may persist for one or several months or more.

The symptomatology is manifold, its character depending upon the system chiefly affected by the toxins, and upon the localization of the metastases. The course may resemble that of typhoid fever; involvement of the nervous system with delirium and coma may suggest meningitis; or multiple arthritis with endocarditis may simulate acute articular rheumatism.

The onset is usually acute, with high fever, and often a chill. Occasionally there is a step-like rise of temperature. The *fever* is intermittent, remittent, or continuous. Sometimes all three types are seen in a single case. The continuous form is that generally associated with acute staphylococcic septicemia, the intermittent with infections due to the colon bacillus and the gonococcus, while any type of fever may accompany streptococcic septicemia.

Brain.—Cerebral symptoms are common, especially headache and nocturnal delirium, and in the rapid cases, stupor or coma. Meningitis often develops as a terminal event in pneumococcic septicemia and occasionally in the other infections. There may be meningismus, *i. e.*, the signs of meningitis without changes in the spinal fluid and the meninges except for the hyperemia which is observed at autopsy. Metastatic abscesses may form in the brain.

Heart.—The rise in the *pulse rate* is usually proportional to the degree of fever; rarely there is a relative bradycardia, as in typhoid fever. The *heart*, as a rule, shows no striking changes. If endocarditis sets in, a murmur is audible in about 60 per cent. of cases. Soft mitral systolic murmurs are often detected in the absence of endocarditis, and may be ascribed to the fever or to the anemia. Pericarditis may occur.

Blood.—The blood usually shows a leukocytosis. Not infrequently, however, the white count is normal or, rarely, subnormal, but in such cases

there is almost always an increase in the percentage of polynuclear cells. Usually a secondary anemia of moderate degree develops, and occasionally there is a marked and rapid loss of red cells.

Lungs.—Bronchopneumonia is not uncommon. Metastases do not usually give rise to definite signs of consolidation, but there is cough, with an increased respiratory rate, and a friction-rub. Empyema occasionally supervenes.

Abdomen.—Vomiting and anorexia are common symptoms. Diarrhea of an obstinate character occasionally develops, with or without inflammatory lesions of the gut. The *spleen* is almost constantly enlarged, and is usually palpable. Pain and tenderness over this organ, sometimes accompanied by a friction-rub, are evidences of infarction. The *liver* is little, if at all, enlarged. Infarction of the *kidney* often leads to severe sudden pain and tenderness in the loin or abdomen.

The Urine.—While a febrile albuminuria is very common, signs of acute nephritis are unusual except in subacute bacterial endocarditis. If infarction of the kidney takes place, there may be hematuria. Pyuria, as a consequence of metastatic pyelonephritis, is occasionally met with. Cultures of the urine often show that it contains the invading organism.

Genitalia.—Occasionally painful swelling of the testis or epididymis results from metastasis.

Eyes.—Retinal hemorrhages are not uncommon; less often round white spots due to minute emboli form in the retina. These lesions do not produce symptoms. Metastatic panophthalmitis with destruction of the eyeball is rare. Optic neuritis is uncommon, except in association with subacute bacterial endocarditis.

Muscles.—Metastatic abscesses frequently develop in the muscles, but are usually too small to be of clinical importance.

Bones.—Pain and tenderness of the long bones on percussion is fairly common, and is a symptom of some diagnostic value. Localized periostitis may occur. In septicemia secondary to acute staphylococcic osteomyelitis the local process dominates the picture, but when metastatic osteomyelitis is due to other organisms there are often no symptoms.

Joints.—Arthritis is common, especially in streptococcus infections. The large joints are those most often involved, and sometimes several in succession may be affected. The lesions frequently, but by no means always, suppurate.

The Skin.—Skin rashes, which frequently appear, are of great diagnostic importance. The commonest variety consists of small cutaneous hemorrhages or petechiæ, in either large or small numbers; similar spots may develop on the palpebral conjunctivæ. Erythematous rashes—fleeting diffuse pink areas—are common, but a scarlatiniform eruption is rare except when there is true scarlet fever. In staphylococcic septicemia there often form small vesicles with a red halo, which rapidly become pustular. Types more rarely seen are bullous, urticarial, papular, and pustular in character. The eruption of pyocyaneus septicemia is characteristic and consists of hemorrhagic spots which become necrotic in the center and suppurate. Jaundice, of hematogenous origin, is an occasional feature. The subcutaneous tissues may be the seat of abscesses.

Diagnosis.—The possibility of septicemia should be considered whenever fever is associated with infected wounds, childbirth or abortion, and when

it persists in mastoiditis or is of obscure origin. A history of a recent furuncle or infected wound, an otitis media or sore throat, may give a valuable clue. Careful search should be made for the portal of entry, which may be in the skin, throat, teeth, ears, the accessory sinuses, the alimentary and urinary tracts, or the genitalia. The possibility of *osteomyelitis* should be borne in mind and the long bones examined. *Blood-cultures* are a very important and sometimes essential method of diagnosis. If negative at first, they should be repeated; they are most likely to be positive if the blood is taken when the fever is at its height. Since the skin rashes (especially the petechiæ), retinal hemorrhages, arthritis, embolic phenomena, and metastatic abscesses are rare in the diseases often confused with septicemia, their presence is of great diagnostic importance.

In differential diagnosis the chief diseases to be considered are typhoid fever, miliary tuberculosis, and acute articular rheumatism. *Typhoid fever* is usually easily recognized by its gradual onset, the dull facies, the presence of rose-spots, and the laboratory findings. Enlargement of the spleen is common to both diseases. The occurrence of endocarditis, arthritis, petechial or vesicular rashes, emboli, and metastatic abscesses is very rare in typhoid. On the other hand, intestinal hemorrhages and rose-spots are rare in sepsis. The presence of leukopenia with relative lymphocytosis excludes the possibility of septicemia, in which the count is sometimes low, but with a predominance of the polynuclears. *Acute miliary tuberculosis* is recognized by the presence of a focus of tuberculosis in the body, by the dyspnea, cyanosis, and fine râles in the lungs in the pulmonary type, and by examination of the spinal fluid in the meningeal type. *Tubercle bacilli* are rarely present in the sputum, but are sometimes found in the urine. The blood usually shows a leukopenia with increase in the number of polynuclears. The presence of tubercles in the choroid is conclusive evidence, but is rare except in the last few days of life. *Acute articular rheumatism* is likely to be confused with the arthritis of septicemia. It is never suppurative, however; tends to involve the joints one after another, remaining in each only a few days; and is associated with fever and pain, which usually yield promptly to treatment with salicylates. Embolic phenomena and chills do not occur, the spleen is not palpable, and the blood-cultures are, with rare exceptions, negative. *Malaria* is easily excluded by examination of the blood and by the failure of quinin to abolish the fever. The manifestations of a hidden *focus of suppuration* may be confused with those of septicemia, especially in the case of *gall-stones* in the common duct and *perinephric abscesses*. Acute *pyelitis* may be a cause of obscure fever, and in children may be unaccompanied by pain and tenderness over the kidney; examination of the urine determines diagnosis. Occasionally *Hodgkin's disease* or *cancer* may cause chills and intermittent fever.

Prognosis.—The mortality in septicemia is high, varying from 60 to 80 per cent. It is highest in infections with the pneumococcus (exclusive of the bacteriemia of lobar pneumonia), and lowest in those with the colon bacillus. In general, the larger the number of colonies in the blood-culture, the worse the outlook. The prognosis is better when a focus of continued infection can be removed, as in sinus thrombosis secondary to mastoiditis, or in some cases of puerperal infection.

Treatment.—The primary focus should be removed, if possible, in

order to prevent continued infection of the blood. Absolute *rest in bed* is necessary. The *food* should be nutritious and easily digestible; a high caloric diet is desirable if digestion permits. *Fluids* should be forced (about 3000 c.c. per day) to facilitate the elimination of toxins. *Hydrotherapy* is useful to control the insomnia and delirium and to reduce the fever. Occasional doses of *hypnotics* or of morphin may be required. *Digitalis* is of little value, except in case of cardiac decompensation. The *transfusion of blood* (300 to 500 c.c. at intervals of four to seven days) is useful to combat the anemia.

Protein therapy has been employed, with varying results. It produces its effect by the so-called "protein-shock," the injections being followed by a chill and rise of temperature. The colloidal metals and peptone solutions are the preparations usually employed, and are given intravenously. The treatment is of doubtful value.

Specific Therapy.—The effectiveness of *antisera* varies with the type of organism concerned. In the case of the streptococcus no benefit is to be expected except in scarlet fever, where the new serum of Dochez produces results which appear to be comparable to those obtained with antitoxin in diphtheria. Antimeningococcus serum has curative value in meningococcus septicemia Type I antipneumococcus serum is usually not effective against the corresponding type of septicemia. No antisera are available for staphylococcus, gonococcus, or colon bacillus infections. *Convalescent serum*, or whole blood (100 to 300 c.c. injected intravenously), is of distinct value in streptococcus sepsis, especially in scarlet fever, but it is essential that it come from a patient infected with a similar strain of the organism.

Vaccines are of no use in acute sepsis. In the chronic type, in the absence of endocarditis, they may possibly do good occasionally, and it is consequently permissible to try them, using always autogenous preparations in small doses every few days.

Intravenous Drug Therapy.—A chemical substance which will kill bacteria in the blood without injuring the host has long been sought, but as yet in vain. Mercurochrome 220, the most recently discovered of these bactericidal drugs, is highly useful in localized infections, but has proved to be worthless in the treatment of septicemia. (The same applies to the intravenous use of other antiseptics, such as carbolic acid.)

Wilder Tileston.

FOCAL INFECTIONS

The great importance of focal infections came to be recognized largely because of the pioneer work of Billings. As the subject is so wide and varied only a brief discussion is possible here.

Definition.—The term "*focal infection*" is usually applied to a localized infection which produces symptoms in other parts of the body, but without showing bacteria in the blood.

Etiology.—The deleterious effect is produced by the repeated absorption of bacteria or their toxins into the circulation. The site of the meta-

static lesion depends upon the existence of a region of lowered resistance, or upon the selective action of the toxin or bacterium. By far the commonest organism involved is the *streptococcus;* the *gonococcus, staphylococcus,* and *pneumococcus* coming next in order.

Morbid Anatomy.—The focal infection may be localized in any part of the body, but most commonly occurs in the tonsils or teeth, the former in both young and old individuals, the latter rarely in children, but very often in adults. Other important locations are the accessory nasal sinuses, the genito-urinary tract, the gall-bladder, and occasionally the appendix.

Symptoms.—Many conditions have been shown to be the result of infective foci, and their number increases almost every year. The most common are *subacute* and *chronic arthritis* of the infectious type, *neuralgias,* especially of the face and arms, *myalgia* and *myositis, acute* and *subacute nephritis,* and *inflammatory lesions* of the eye, such as iritis, keratitis, and choroiditis. Gonococcal arthritis is an excellent example of focal infection. Other less common diseases which may be caused in this way are erythema nodosum, phlebitis, perinephric abscess, and possibly pyelitis and herpes zoster. *General debility,* often accompanied by gastro-intestinal disturbances, may be brought about in this way. Moreover, a focal infection may lower the resistance to disease of which it is *not* the cause; and removal of foci may therefore be an important measure in the treatment of diabetes, tuberculosis, syphilis, etc.

The *examination* of all patients with such diseases should include a careful search for foci, and *x*-ray examination of the teeth and often of other parts.

Prognosis.—Removal of the primary focus is usually followed by recovery, provided the damage has not been irreparable. The improvement may be rapid or gradual, and is often preceded by an exacerbation of the symptoms because of auto-inoculation during operation. The prediction of recovery should be made with caution and promise of cure should not be held out in diseases of which the cause is still unknown, such as chronic hypertrophic and atrophic arthritis, hyperthyroidism, and essential hypertension.

Treatment.—Once discovered, the focus should be removed by appropriate therapy. If the tonsils are acutely inflamed, it is better to wait several weeks after the subsidence of the fever before removing them; the same applies to all operative procedures in the presence of the acute infectious diseases. If many teeth are infected, only one or two should be extracted at first, the rest after a fortnight. Very anemic patients should receive a transfusion of blood before operation.

The use of *autogenous vaccines* is justifiable *after* operation, though seldom necessary; it is of little value as long as the infective focus is active.

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RHEUMATIC FEVER

(*Acute Rheumatic Fever, Acute Articular Rheumatism, Acute Rheumatism, Polyarthritis Rheumatica*)

Definition.—Rheumatic fever is a disease of undetermined etiology characterized by fever and a toxic state, and by the presence in certain organs of the body of small disseminated focal lesions of a proliferative type. In acute stages there is also an exudation in and about the joints, and sometimes in the pleuræ and pericardium. A further characteristic is the tendency for the febrile and arthritic symptoms to disappear when the patient is given large doses of compounds of salicylic or phenyl cinchoninic acids.

Incidence.—While the acute disease is fatal in only a small proportion of cases, the cardiac sequelæ of rheumatic fever are among the most important of medical conditions. Occurring chiefly in children and young adults, the cardiac disease arises when the victims should be economic assets rather than liabilities. In children and adolescents of school age rheumatic carditis is the largest single cause of death.

The incidence of rheumatic fever and the total years of suffering are not reflected in mortality statistics. Furthermore, as it is not reportable, we are unable to compare its relative frequency with tuberculosis or pneumonia; nevertheless, experience has shown that it is among the most important of diseases.

Morbid Anatomy.—The typical pathological unit is a submiliary nodule close to small blood-vessels in interstitial connective tissue. Early there is a central area of fragmented collagen fibers and coagulated serum. This is soon encircled by large cells having a basophilic cytoplasm and large vesicular nuclei, frequently multiple; their origin is probably from the endothelium of small blood-vessels and perivascular spaces. Mixed with them are a few lymphocytes and occasional polymorphonuclear leukocytes. Later plasma cells and fibroblasts gradually replace the typical large cells; and the submiliary nodule is gradually replaced by a microscopical scar. There is also a fine proliferative vasculitis.

This focal lesion is most typical in the Aschoff body found in the myocardium; comparable lesions elsewhere are modified by the peculiarity of the tissue in which they occur. Thus the subcutaneous rheumatic nodule may be considered as a conglomeration of submiliary nodules arising in an area where fairly large masses of tissue can respond to the localization of the rheumatic virus. Similar small lesions occur in the periarticular tissue and synovial membranes; but there is, in addition, a marked increase of viscid synovial fluid containing fibrin and wandering cells. The periarticular tissues are also very edematous; hence, the arthritis is a combination of focal, proliferative, and diffuse exudative lesions. While the exudate disappears quickly, the proliferative lesions are but slightly influenced by the administration of salicylates.

In involvement of the pericardium and pleura the exudate is serofibrinous; in pericarditis the fibrinous exudate may be very extensive, and the normal endothelial lining of the pericardium be entirely destroyed and eventually replaced by the organization of this exudate into fibrous tissue with obliteration of the pericardial cavity. In pleurisy there is relatively less fibrin in the exudate and fewer adhesions than are usually seen following pericarditis.

In chorea minor, which may be considered as a rheumatic affection of the central nervous system, there are disseminated focal endo- and perivascular lesions in various portions of the brain, together with some neuroglia increase. These foci may seem to have little similarity to Aschoff bodies, but when it is understood that the brain is capable of only a moderate and relatively simple response to focal insult of the type encountered in rheumatic fever, the parallelism is more apparent.

Rheumatic valvulitis, ordinarily called endocarditis, is more clearly understood if considered from the viewpoint already advanced. Grossly there is a deposit of small grayish-pink verrucæ along the surfaces of the valves at the lines of contact of opposing cusps, together with thickening of the valves. Microscopically, the vegetations consist of fibrin enmeshing various cellular blood elements deposited on a portion of the valve from which the endothelium has been denuded. In the substance of recently involved valves, as yet practically free of verrucæ, we have seen areas closely resembling Aschoff bodies. Small foci of proliferative inflammation with rapid vascularization are usually seen. It is, therefore, probable that the interstitial inflammation of the valve is the primary process[1] and that the thrombotic verrucæ are secondary in nature; their location is probably the result of mechanical trauma which causes the valvular endothelium, already swollen and proliferated because of the underlying inflammation, to be destroyed at the points of most violent impact of opposing cusps. Healing is effected by vascularization of the verruca and by scar formation in both the valve and vegetation; the endothelium at the bases of the verrucæ grows over the surface; and a thickened, scarred, less flexible valve is the usual result. This valve, moreover, is a *locus minoris resistantiæ;* either because of its vascularity or because tissue once involved exerts a positive attraction for a new infection of the same type, or, finally, because the "virus" remains locally latent but ready to renew its activity when the general resisting processes are depressed. Thus the valves of a patient who has suffered from two or more attacks of rheumatic fever show evidence of the previous attacks in scar formation and increased vascularity and of the last attack in new focal proliferative lesions and recent vegetations.

Submiliary nodules are not infrequently found under the mural endocardium, at times in great numbers in the left auricle, as recently described by MacCallum. Pappenheimer and Von Glahn also report them in the adventitia of the aorta, with small focal scars in the media and collections of large cells about the vasa vasorum.

Etiology.—Predisposing Causes.—Rheumatic fever occurs most frequently in the temperate and subtropical zones. The polyarthritic form seems to be the more prevalent in regions bordering on large bodies of water. It is apparently more common along the north and middle Atlantic seaboard than in the Great Central Basin of the United States. Mitral stenosis, however, is frequently encountered inland; and it may be that the manifestations of rheumatic fever vary under different physical surroundings.

As with many other infectious diseases, there are cycles of years in which the condition is more or less prevalent. Newsholme observed the peaks of these cycles, occurring every four to six years, to be coincident with periods of low rainfall and consequently dry soil. There is also a

[1] This point is especially stressed by Carey Coombs.

definite seasonal variation: in America and on the continent of Europe the majority of cases occur in the late winter and spring; in England, on the other hand, the incidence is somewhat greater in the autumn.

Many instances are recorded of several cases in different families successively residing in the same house, possibly due to dampness or other deleterious environmental factors. In maritime cities relatively more cases come from districts close to the water front, possibly because poorer persons dwell there; for, apparently, poverty, malnutrition, and unhygienic surroundings furnish the most favorable human soil for the development of this infection. Many cases are seen, however, among well-to-do members of society.

Recent investigators have reported that some rheumatic condition could be detected in the families of one-half or more of their patients. The significance of this is probably an hereditary lack of resistance or lack of capacity to develop an immunity to certain types of infection. It has been suggested by Draper and others that certain anthropological types are especially prone to rheumatic fever.

It is usually stated that the majority of cases occur within the first three decades of life. Although the disease is occasionally found in the very young, it begins to appear more frequently at four or five years; from this time on the relative incidence varies according to the class of patients seen by any given observer. The importance of the rheumatic infection later in life, however, is brought out by Pappenheimer and Von Glahn's tables; 45 per cent. of their fatal cases occurred in patients over thirty years of age.

Sex Distribution.—While polyarthritis is seen more often in men than in women, if we include all manifestations of the disease, females are affected more often than males. This is especially illustrated by the greater frequency of mitral stenosis among women.

Focal Infection.—Recently the relation of focal infection to various forms of rheumatism and systemic diseases has been much discussed. It is claimed that the focus in whatever organ localized is the nidus whence small amounts of the infectious agent are constantly or intermittently fed into the blood-stream, from which it is deposited in the tissues. From a statistical standpoint diseased tonsils are more frequent than other foci of infection in patients with rheumatic fever. Removal of an infected oral focus, indeed, not infrequently leads to a surprising disappearance of symptoms; but more often the general disease persists. This may be due to failure to locate the original focus, or to the probability that the inflamed joints or viscera have become new foci.

The immediate causative agent has not been definitely determined; nor has the typical disease been reproduced experimentally by inoculation of laboratory animals. It may be that the lower animals are incapable of responding in the same manner as man to the hypothetical virus, or that this virus has not been discovered. Many observers believe the *Streptococcus rheumaticus* to be the causative agent; more think it is a secondary invader. Our own observations at present indicate that the bacteria occasionally recovered from the blood or nodules are a heterogeneous group of non-hemolytic streptococci, usually called viridans, with no common biochemical or immunological relationship; in several patients we have found two or more distinct strains of viridans and occasionally hemo-

lytic streptococci in addition. Generally the causative agents of a specific disease fall into one or, at most, a very few immunological types. The heterogeneity of the streptococci recovered has forced certain observers to consider rheumatic fever to be a peculiar mode of response on the part of the patient to a number of different types of stimuli, rather than the effect of a uniform stimulus or causative agent. Some even consider it a phenomenon of hypersensitiveness of the type encountered in serum disease. These possibilities are briefly mentioned to emphasize our present uncertainty as to the exact nature of the disease.

Symptoms.—While this disease is usually considered as one having pyrexia, toxemia, and migratory polyarthritis as its main features, this description is one of convenience only, and other essential features must be kept in mind if its nature is to be clearly comprehended. The symptoms of rheumatic fever, moreover, as seen today are usually markedly altered by antipyretic drugs, which, while affording comfort, also carry with them the danger of blinding both the physician and the patient to manifestations of infection in some important organ.

Prodromata.—In over half of the patients the acute onset is preceded by sore throat or tonsillitis. In others, there is a history of acute infection of the upper respiratory passages or lungs. Often there are malaise, anorexia, loss of weight, and diminished capacity for work. In a minority of instances there are no prodromal symptoms, but the onset may be precipitated by a chilling or other depressing influence.

Within the period of twenty-four hours the acute attack is usually well developed, with a fever of 102° to 104° F., rapid pulse, profuse perspiration, severe prostration, and polyarthritis. It is rare for the inflammation to begin simultaneously in all of the joints; those most subject to stress and strain are first affected. Initially monarticular arthritis is rare; it is more common to have the symmetrical joints simultaneously affected. The striking feature of the arthritis is its migratory character; new joints are involved in rapid succession. Various modes of extension described by different observers need not be here detailed. While any joint in the body may be inflamed, the large joints are most often implicated; some claim that early involvement of the fingers and toes prognosticates a more chronic type of disease.

A single involved joint usually manifests all the signs of acute inflammation, viz., pain, tenderness, swelling, heat, and local redness. The swelling is due both to an effusion into the joint cavity and to edema of the periarticular structures. Pressure from exudate probably accounts to a considerable degree for the pain, because there is often marked local relief following the aspiration of fluid from a joint. Because of tenosynovitis the local manifestations must be considered not only as an arthritis, but as an inflammation of any structure in proximity to a synovial membrane. While the turbid fluid aspirated from these joints shows a marked increase in cells, at times 20,000 to 30,000 per cubic millimeter, suppuration does not occur unless there is secondary infection by pyogenic bacteria. Disappearance of arthritis, especially in children and young adults, is accompanied by complete restoration of function without gross alteration in structure; in older people, on the other hand, slight morning pain and stiffness often persist for several weeks.

The polyarthritic form of the disease may be conveniently divided

into monocyclic, polycyclic, and continuous. In the first there is a single cycle of fever lasting from ten to fourteen days; the arthritis spreads from one set of joints to another, with an increase in pyrexia as each new set is involved; each joint is inflamed from four to six days, then recovers and is not again affected; after involvement of few or many of the joints the fever decreases, the arthritis diminishes, and the patient recovers without further manifestations. In the polycyclic form, on the other hand, following a single cycle such as described, there may be recurrence of another cycle of the same type, or joints that have recovered may again become inflamed before completion of the first cycle and thus the two be superimposed. The administration of salicyl shortens these cycles, but persistence of infection may be shown by the recurrence of arthritis and fever as the influence of the drug wears off. In the continuous form the patient always presents some indication of active infection, often varying in intensity from time to time. In both the polycyclic and continuous forms the physician should be especially alert to detect serious involvement of the heart.

Cardiac involvement is one of the most common features of rheumatic fever and is detected in proportion as our methods of examination are refined and applied. Thus, daily or biweekly electrocardiograms showed transitory abnormalities in over 95 per cent. of our patients. These variations, occurring at any time, may be the chief signs of a re-awakening infection. While such graphic records are impossible in all cases, repeated careful physical examinations will frequently reveal evidence of cardiac involvement. Obvious signs of cardiac embarrassment are easily detected and need not be here discussed, but less marked signs require consideration. Precordial pain and hyperesthesia point to myocardial involvement usually quite unaccompanied by pericarditis. Gross changes in the size of the heart, detectable by percussion, are indicative of marked dilatation or of pericardial effusion. Significant roentgenographic alterations in the size of the heart are less frequent than would be expected.

A diffuse apical impulse, wave-like in character, indicates that the heart muscle is not contracting normally. One can, at times, feel at the apex, or just above and mesial to it, an extra impact synchronous with an intensified third heart sound. This gives the palpatory evidence of a gallop, more easily heard; when felt, however, it is a sign of unusual cardiac action.

While it is impossible to be dogmatic concerning the interpretation of abnormal auscultatory signs, much valuable information can be gained by listening to the heart daily. Cardiac rate will be discussed later. A change in auscultation rhythm is fairly common; most frequently it is expressed as a gallop apparently due to an accentuation of the third heart sound, which is at times as intense as the second sound. Gallops usually come and go, hand in hand with other evidence of cardiac involvement. While most common in children and adolescents at an age when a third heart sound is most readily detectable, still they are often present in adults. The tick-tack rhythm of embryocardia is usually accompanied by obvious cardiac dilatation and other evidence of heart failure, and is always a serious omen. Aside from the usual sinus arhythmia of children, irregularities in rhythm are due to premature contractions, to heart block, usually partial, or to auricular fibrillation. Sometimes extrasystoles are frequent and regular enough to give coupled beats, again they occur in uneven groups

suggesting auricular fibrillation, at other times they appear only once or twice a minute. The regular dropping of a ventricular systole every 4 to 7 beats points to partial heart block; this suspicion can be confirmed by electrocardiograms or polygrams. Partial blocks usually persist only a few days. Rarely complete heart block with bradycardia is encountered.

Complete irregularity, due to auricular fibrillation, occasionally occurs, and indicates a severe degree of cardiac involvement; it is ordinarily accompanied by pericarditis and usually is not persistent. Some patients after recovering have resumed their normal laborious occupations without a return of cardiac irregularity.

Murmurs detected during the course of an attack of rheumatic fever are difficult of interpretation, especially when systolic in time. Such systolic murmurs, audible over the lower left precordium, are frequent and usually explained as due to dilatation of the valve rings resulting in a slight relative insufficiency. If we predicate that there is an interstitial valvulitis with edema and subsequent deposition of verrucæ, we must conclude that some of the regurgitation, at least, is due to imperfect approximations of the leaflets. Many patients have a very soft blowing diastolic murmur along the left sternal margin from the third to the fourth interspaces, at times audible at the apex, best heard by direct auscultation, and unaccompanied by low diastolic pressure. Occasionally such murmurs recur, with other evidences of renewed infection. Sometimes after recovery they disappear permanently; again obvious signs of aortic insufficiency eventually develop. The final significance of these murmurs must often be determined by studying the patient for months or years.

Doubtless during the early period the tissue is often prepared for the ultimate development of deformed valves. Crippling degrees of scarring, however, seem to depend upon the persistence of infection or the repeated recurrence of infection in the valves. Not infrequently loud murmurs persist without cardiac embarrassment in patients who have fully overcome their infection; again only slight physical signs of valvular defects are found in others who are the subjects of marked cardiac insufficiency. The degree of myocardial involvement, therefore, is as significant as the thickening of the valve or the dilatation of its ring.

Pericarditis in rheumatic fever practically always is accompanied by an underlying myocarditis, hence the importance of its detection. Precordial pain, occurring in a rheumatic fever patient, is probably due more to a myocardium laboring under great handicap than to inflammation of the covering membranes. One who awaits the appearance of precordial pain before suspecting pericarditis will fail to detect many instances, for pericarditis often is unaccompanied by pain. More significant is a to-and-fro friction-rub, which, if of a double shuffle character, is pathognomonic. Such rubs may persist for days or occasionally last only a few hours. With the accumulation of large amounts of fluid in the pericardial sac the rubs decrease or disappear; they often persist, however, in spite of the outpouring of exudate. The high fibrin content of these exudates may explain in part the persistence of a rub and the insignificant reduction in the areas of precordial dulness and flatness after paracentesis. Accumulation of exudate is indicated by increase in the area of precordial flatness, and by a triangular area of marked dulness or flatness posteriorly in the region of the angle of the left scapula, with distant bronchovesicular breath-sounds and egophony

over this area. There occur also general symptoms and signs of weakened heart action dependent both upon pressure from accumulated fluid and upon concomitant myocarditis. The patient should be followed, upon recovery, for signs of adhesions between the two layers of the pericardium, for such adhesions are often the cause of severe permanent cardiac insufficiency.

The *pulse* generally reflects the condition of the heart; hence, alterations in cardiac rhythm and rate are immediately indicated in pulse records. As alterations in rhythm have already been mentioned, only rates or special features need be here discussed. Early in polyarthritic forms of the disease acceleration in rate is proportional to the fever, later it is indicative of myocardial damage. Often a relapse in which the heart is the principal site of infection is indicated by rapid pulse. If a high pulse rate persists in spite of normal temperature or low-grade fever, myocarditis should be suspected. Marked and persistent increases in rate following slight exertion are very suggestive of injury to the heart muscle. If, on the other hand, physical exertion induces a quickened pulse which soon returns to its original rate or slower, it shows that the weakened heart action is probably atonic in origin and susceptible of improvement under regulated exercise. A pulsus paradoxus sometimes accompanies severe pericarditis.

Pleurisy, occurring in 5 to 10 per cent. of patients, is more frequent on the left side, when it usually accompanies pericarditis. It generally indicates a severe rheumatic infection, but occasionally is the chief evidence of a relapse in a patient who has had a polyarthritis weeks or months before. Rarely it is the initial manifestation of rheumatic fever, and probably certain cases of so-called idiopathic pleurisy are rheumatic in origin.

The onset of pleurisy is heralded by intensification of the signs of general infection, and by characteristic, sharp, stabbing pain on inspiration. With the accumulation of fluid the pain decreases, but tachypnea, at first the result of pain, becomes more accentuated, due to the compression of lung and often to a concomitantly weakened myocardium. Pleural exudate, as a rule, need not be aspirated, but at times, with marked embarrassment of respiration, *paracentesis pleuræ* adds much to the patient's comfort.

Pneumonia, lobular rather than lobar in distribution, occasionally occurs in patients who are seriously sick and who have, in addition, severe carditis and pleurisy; the physical signs are confusing, as they may be caused by a combination of consolidated lung, passive congestion, and pleural effusion. Sometimes the onset of pneumonia is indicated by general symptoms of renewed infection; again, it is unsuspected by the physician until after repeated careful examinations of the lung. The expectoration of mucopurulent or blood-streaked sputum is a symptom of diagnostic import.

Upper Respiratory Passages.—Inflammation of some portion of the upper air passages is a feature in the majority of cases of rheumatic fever. In addition to the prodromal tonsillitis, each relapse is often initiated or accompanied by this condition. Many rheumatic children have chronically diseased tonsils, with enlargement of the satellite cervical lymph-nodes. These abnormal nodes and persistent redness along the anterior faucial pillars are often more indicative of chronic irritation of the tonsils than is the simple protrusion of these structures into the pharynx. Accompanying

acute polyarthritis there sometimes occurs a diffuse pharyngitis without much exudate; this responds to salicylates in the same manner as does the arthritis. Infections of the accessory nasal sinuses, both acute and chronic, are found in certain rheumatic fever patients; and at times there seems to be a direct connection between the general disease and this local infection. Laryngitis occurs usually as a diffuse catarrhal inflammation extending from a pharyngitis; occasionally, as discrete nodules on the vocal cords; and, very rarely, as an acute edema of the epiglottis and vocal cords with a dangerous stenosis of the larynx.

Respiration.—In all patients there is an increased respiratory rate parallel with the fever and quickened pulse; but disproportionately rapid breathing may accompany pneumonia, pleurisy, or carditis. Tachypnea as a concomitant of rheumatic carditis is especially noticeable in children, in whom the rate may be from 50 to 70 per minute without any evidence of pulmonary infection. Attacks of rapid breathing in adults may accompany extensive, severe polyarthritis and merely reflect the extreme pain the patient is suffering; in such instances the relief of pain by splinting or anodynes is followed by a decreased respiratory rate.

The *cutaneous manifestations* of rheumatic fever consist of various exudative dermatoses, but none is absolutely typical of the disease, as similar rashes are seen in other infections and apparently as independent conditions. Various types of erythema multiforme are the most common; often the rash starts as flat papules, rapidly increasing in size, and clearing in the centers; finally the migratory borders of several lesions fuse into an extensive marginate erythema. Frequently the evolution and resolution occur within a few hours. Often such rashes recur for weeks or months. They commonly do not itch, hence may be easily overlooked. Occasionally purpura is seen. Whether the syndromes included under Henoch's purpura and Schönlein's disease are of rheumatic origin it is impossible at present to decide.

Erythema nodosum is an occasional complication; sometimes there is only a single outbreak; in other patients there are repeated crops of painful subcutaneous indurated areas, with the overlying skin at first red, later purple and greenish.

Sudaminal eruptions following the severe sweating are one of the usual manifestations of a severe, febrile intoxication.

Subcutaneous nodules, one of the most important of the "rheumatic series," indicate that the patient's response to the virus is chiefly proliferative in nature and wide-spread in distribution, with concurrent myocarditis and valvulitis; hence, their existence is considered of serious if not of fatal prognostic import, but many patients with them recover and return to a normal useful life for years. Being usually painless, they must be diagnosed by inspection and palpation over the extensor aspects of joints, along the spine and over superficial flat bony surfaces such as the skull, scapula, olecranon, patella, and malleoli; they may also be seen in superficially located tendons and tendon sheaths. They are best demonstrated by placing the patient between the light and the examiner, and having the skin over the suspected area tightly stretched, usually by flexing the joint. They then appear as white or light gray nodules, from 1 to 10 mm. in diameter, connected with the deep fibrous tissue and not with the skin which is freely movable over them. Palpation reveals them as hard and only slightly

movable when the joints are flexed, somewhat more so when extended. If in the scalp or over the bellies of muscles, they must be detected by palpation; but, as a rule, let it be emphasized, they are best found by inspection. Conglomerate masses are often seen. Each nodule persists for from a few days to several weeks, and although of rapid evolution it usually undergoes more gradual resolution. Often they occur in successive crops, so that in a given area nodules of various ages may be found. They appear while the patient is saturated with sodium salicylate or neocinchophen, and, unlike rheumatic arthritis, do not disappear quickly when the patient is placed fully under the influence of these drugs.

Blood Picture.—Moderate to severe degrees of secondary anemia produce a washed-out, waxy appearance in patients who have suffered very severe or prolonged attacks. Erythrocyte counts and hemoglobin estimations usually confirm what has been indicated by simple inspection.

The plotting of leukocyte curves from counts made every five to seven days is useful in studying the course of the disease. With severe polyarthritis and fever there is a leukocytosis of from 15,000 to 25,000, which decreases with the recession of symptoms, either spontaneous or drug induced. In the monocyclic infection the leukocytes return to and remain normal after a few weeks. In the polycyclic and continuous forms, on the other hand, there is usually, though not always, a low-grade leukocytosis, which becomes more marked prior to a clinical relapse. This leukocytosis often persists even in a patient under the influence of antirheumatic drugs, when it is one of the most important indicators of a slumbering, but easily awakened, infection.

Nervous Manifestations.—With hyperpyrexia rheumatica there is always delirium, followed by coma. In patients with ordinary fever one occasionally encounters delirium, which may either pass into coma or disappear; subsequently the patient may have a psychosis with delusions, and require prolonged institutional treatment. Large doses of sodium salicylate in susceptible individuals occasionally lead to acute delirium with delusions of persecution.

Chorea is one of the grave manifestations of rheumatic fever in children. Accompanying practically all fatal chorea there is typical rheumatic myocarditis and valvulitis. Not infrequently polyarthritis and severe carditis occur with chorea; again, subcutaneous nodules and chorea are the only outstanding features. In many patients, on the other hand, chorea occurs alone with only slight or no fever, but the next relapse may be accompanied by some other member of the rheumatic series. Several recent studies show that chorea in a rheumatic child indicates a very persistent type of infection; the recognition of this should result in greater efforts to shield these children from great stress and strain and from the different infections known to increase the liability to rheumatic relapses.

Severe polyneuritis rarely complicates rheumatic fever, but slight pain along the peripheral nerve trunks is not infrequently a sequel of polyarthritis, especially in older people, in whom it is often difficult to distinguish the pain and stiffness due to a residual myositis and tenosynovitis from that caused by neuritis.

Kidneys.—Albuminuria and cylindruria often accompany a high fever and disappear as the temperature approaches normal. Large doses of salicylates are often followed by hematuria—usually microscopical—and

the outpouring of small cast-like bodies. Neocinchopen in large doses may also be followed by definite urinary signs of renal irritation. Urinary findings are, therefore, important guides in the administration of antirheumatic drugs. The urine is frequently concentrated, and shows a heavy deposit of urates on cooling. Concentration is due to water loss from the lungs and skin; and an increased output of urates, due to lowering of the renal threshold, is one of the pharmacological effects of the antirheumatic drugs. Although rare, a true acute nephritis occasionally accompanies rheumatic fever; when encountered the physician must proceed cautiously with these drugs.

Nutrition.—In all types of rheumatic fever the general nutrition of the patient suffers. In the acute forms the weight drops rapidly; with recovery it is regained quickly. In the subacute and chronic disease, while the loss may be more gradual, it is often correspondingly difficult to repair. The weight curve is, therefore, an important guide to the patient's condition. Continually falling or remaining subnormal, it indicates that he is not overcoming the infection; a sudden drop often heralds a relapse. A steadily rising curve is favorable, but should not be considered the sole guide to improvement, because persistent low-grade infection is seen even in overweight patients. Those taking large amounts of antirheumatic drugs often show a marked drop in weight due to severe sweating. Occasionally when these drugs are given to the point of distinct renal irritation there is a sharp increase in weight due to edema.

Rheumatic fever in children, unless acutely fatal, practically always runs a subacute or chronic course. The various types of manifestations shown by children—polyarthritis, pleurisy, carditis, chronic tonsillitis, "growing pains," chorea, and subcutaneous nodules—have been designated as the rheumatic series. In general, the combination of acute toxic and exudative manifestations so characteristic of the infection in adults is less marked in children; on the other hand, chronic low-grade intoxication together with focal proliferative lesions furnish the usual picture in the young. Arthritis is less extensive and more transitory; there is usually carditis; relapses are common. Each relapse may be made manifest by only one or two members of the rheumatic series, but over the course of years the entire gamut may be run. With each relapse there are increasing signs of cardiac damage, and unless the resisting capacity of the patient can be made sufficient to throw off the infection permanently, the final picture is one of cardiac failure. A certain proportion of young patients recover, however, with few if any signs of cardiac injury.

Diagnosis.—Because the etiological agent is undemonstrated, and there is no characteristic laboratory test, the diagnosis must rest upon direct consideration of the symptoms, signs, and course of the disease, and upon the elimination of other conditions.

The migratory polyarthritis responding to certain drugs is a feature practically unduplicated by other diseases. Early signs of cardiac involvement, subcutaneous fibroid nodules, persistent undernutrition, low-grade toxic state, and concomitant chorea are all important aids in arriving at a direct diagnosis.

The majority of infections occasionally have arthritis as complications. Secondary arthritis will, therefore, be indicated by an antecedent history of these diseases and by other signs of their persistence. In the case of

most secondary purulent arthritides the causative organism can be demonstrated in fluid aspirated from the joint, and often the immediate microscopical detection of a germ will settle the diagnosis. Patients with gonorrheal rheumatism often have serous polyarthritis, but eventually inflammation becomes persistent in one or two joints, about which the tissues are boggy and from which gonococci can be recovered. Here slight focal destruction occurs, followed by productive arthritis. The presence of gonococci in the genito-urinary tract and of complement-binding antibodies in the blood-serum are differential points.

Following scarlet fever a serous polyarthritis is occasionally seen; the history here is differential. A similar condition sometimes accompanies puerperal sepsis.

In children acute septic arthritis and osteomyelitis may be mistaken for rheumatism. Diagnosis is made by the extremely toxic state of the patient, bogginess of the joint, purulent character of the aspirated fluid, and demonstration of staphylococci or streptococci in the synovial fluid and blood. Hemophilia and scurvy in children also lead to painful swelling of the joints, the nature of which should be determined from other features of these diseases.

Arthritis deformans, or chronic secondary infectious arthritis, sometimes begins acutely with features closely resembling rheumatic fever. The initial and persistent involvement of small joints of the hands, feet and spine, and the comparative freedom from cardiac complications are suggestive features. The persistence of periarticular swelling leading to obvious deformity confirms the diagnosis.

Acute gout must sometimes be considered. Family and personal history, the deposits of tophi in the ears and of urates about the joints, and the almost pathognomonic *x*-ray pictures of the bones should clear up any doubt. A high content of uric acid in the blood without nephritis is conclusive.

Polyarthritis is one of the most striking symptoms of serum disease following antitoxic or antibacterial serum therapy. Marked pain and stiffness of the joints with very slight, if any, effusion, absence of periarticular swelling and redness, a coexistent urticaria, and the history of serum treatment within a period of ten to twenty days serve to determine the nature of the trouble.

Prognosis.—The prognosis as to life is good; the mortality rate during the acute disease is from 3 to 5 per cent. With each decade of life the prognosis improves both as to mortality and liability to permanent cardiac damage. About the age of puberty many patients succumb, as the normal growth at this time seems to impose excessive demands upon the damaged heart, especially when the latter is the site of an active infection. Each recurrence increases the gravity of the outlook. The coexistence of chorea or of nodules with other forms of the disease increase the liability to permanent cardiac damage and eventual death from heart failure. It should be emphasized that if the patient can be induced to overcome the infection completely and does not suffer a relapse he can lead a fairly normal life with damaged valves. The important prognostic factor is his capacity to eliminate completely the infection.

Treatment.—Most important is the understanding by the physician of the nature of the malady and the action of the therapeutic agents. This

is particularly true with rheumatic fever because of the different clinical types, protean manifestations, implication of important viscera, and the existence of drugs favorably influencing symptoms without eliminating the causative agent. Systematic documenting of the various features is most helpful in picturing the course of the infection; the importance of recognizing this cannot be overemphasized, for it is obviously more reprehensible to allow a patient with active carditis to exercise too soon than to keep him inactive too long. If significant records of these patients were kept we would hear less often, "The patient recovered two months ago from rheumatism, but now is suffering from endocarditis."

Rest, relief of pain, attention to nutrition, and regulated convalescence are the chief therapeutic indications. With acute polyarthritis rest is enforced by the pain; when this disappears it must be insisted upon by the physician. While fresh air is beneficial, the patient should be guarded from chilling, which easily occurs because of the severe perspiration requiring frequent changes of the bed and patient's clothing. Frequent bathing and dusting with some absorbent powder helps to prevent maceration of the skin. Swathing the affected joints with flat pads made of cotton covered with gauze affords much comfort. The support of the limbs by pillows so placed as partially to flex the joints provides the most comfortable position.

Large amounts of fluids should be given to encourage the elimination of toxic substances and to replace water lost in sweating. A high calory diet composed of easily assimilable food should be provided; often it is necessary to cater to the patient's taste in order to maintain nutrition. During convalescence it can be coarser and more varied than at the time of high fever.

Drug Treatment.—Practically all of the acute distressing symptoms, except those due to cardiac failure, are relieved by the compounds of salicylic acid. These act as antipyretics and analgesics when given properly. The therapeutic and toxic doses are close together; hence the attendants should watch for the first symptoms of salicyl intoxication. These are ringing in the ears, deafness, nausea, vomiting, and, rarely, delirium; renal irritation must be detected by examination of the urine. Sodium salicylate dissolved in water or in capsules, or acetylsalicylic acid (aspirin) should be given in doses of 1.0 to 1.3 gram (15–20 grains) every hour for from eight to ten doses, or discontinued sooner if toxic symptoms appear. The next day three-fourths of the determined toxic dose may be given, and following this the drug continued at about the same rate. It should be continued until all signs of active infection have been absent for a week or ten days. If well tolerated, it should then be decreased gradually with constant watch for symptoms of relapse. If these recur, the dose must be increased. The combination of sodium bicarbonate with salicylate is a favorite procedure of some physicians; sometimes it seems beneficial. The rectal administration of 120 to 180 c.c. of a 2 per cent. solution of sodium salicylate (x grains to ʒj of water) two or three times daily is sometimes well tolerated when the drug given by mouth leads to nausea. If rectal irritation results, a weak starch solution as a vehicle may be substituted for the water.

There is little if any advantage in intravenous injection of the drug.

Neocinchophen has an effect similar to that of the salicylates and in some instances is better tolerated; the dosage is the same or slightly larger.

It is a useful adjuvant to our therapeutic agents, but its administration must be attended with the same care exercised in giving salicylates.

Occasionally morphin or codein are indicated to control pain, especially in the chest.

In the presence of cardiac insufficiency digitalis should be given, but in doses of approximately one-half those usually ordered for non-rheumatic patients of the same weight and sex, for the existence of active rheumatic myocarditis seems to render the heart more susceptible to the toxic action of the drug.

The treatment of complications follows the same lines as when they occur in other diseases. The pain of severe carditis can often be much alleviated by a light ice-bag over the precordium. If the circulation is much embarrassed by distention of the pericardium with fluid, paracentesis sometimes is of benefit; as a rule, however, the fluid is spontaneously absorbed. The same may be said concerning pleural exudates; only when the breathing space is much decreased is it necessary to aspirate.

Convalescence.—In the management of the patient during convalescence the physician must exercise the greatest care. The rate of recovery is in ratio to the length and severity of illness. No patient should be allowed out of bed until he has been free from fever and other signs of active infection for two or three weeks, during which time he should not have been under the influence of antipyretics; the weight curve should also have returned to normal and the heart rate be fairly slow. The period of being in a chair should be slowly increased; and the patient should be able to sit up four or five hours a day without undue fatigue or re-awakening of the infection before attempting to walk. Then a few steps may be permitted and the distance increased each day; stair climbing should not be attempted until he can walk fifteen or twenty minutes. A good guide to the influence of exertion is gained by counting the pulse immediately before exercise, immediately after, and five minutes later; if it is then as slow as or slower than the original rate it is safe to permit increased exertion; if more rapid, it should be decreased. Reappearance of signs of infection at any time demands a return to complete quiet. In general, the principles and routine that have been elaborated for the treatment of patients with tuberculosis may be well applied to patients with the subacute and chronic forms of rheumatic fever.

Tonsillectomy.—The connection between tonsillar infection and rheumatic fever seems, in many instances, to be intimate enough to indicate tonsillectomy; and in some patients marked improvement follows this operation. A good general principle in the treatment and prophylaxis of a disease like rheumatic fever is to eliminate all foci of infection that may have a depressing influence upon the general capacity for resistance. If tonsillectomy is performed shortly after an attack of the disease, it is well to have the patient under the influence of some antirheumatic drug at the time of the operation, and to regulate exercise subsequently in the same manner as if a relapse had been suffered.

While the few available statistics do not show any great advantage in tonsillectomy from either the prophylactic or curative standpoint, the figures are at present too meager to permit a final judgment; and it is probably best to give the patient the benefit of the doubt.

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DIPHTHERIA

Definition.—Diphtheria is an acute, specific infectious disease caused by the *Bacillus diphtheriæ*. It is characterized by the formation of fibrinous exudates upon the mucous membranes, especially of the throat and respiratory passages, and by constitutional symptoms due to the absorption of toxins from the local lesion.

History.—The disease was known to the ancients. Areteus and Galen described ulcerative membranous lesions of the throat, and Ætius was acquainted with paralysis of the palate, a frequent sequel of diphtheria. Epidemics occurred in the Middle Ages and were described by various English, French, and Spanish writers. Bretonneau gave excellent descriptions of the disease in connection with violent outbreaks that occurred in Tours. He grouped the diseases variously known as putrid sore throat, "cynanche maligna," and angina suffocativa under the term "diphthérite." Trousseau, who confirmed Bretonneau's observations, subsequently changed the name to "diphthérie." The discovery of the *Bacillus diphtheriæ* in 1883 by Klebs and its isolation and identification one year later by Löffler established the definite bacteriological entity of the disease. In 1888 Roux and Yersin demonstrated that the soluble diphtheria toxin could be separated from the diphtheria bacilli by passage through a porcelain filter. The subsequent fundamental researches of von Behring and Ehrlich dealt with the estimation of the strength of diphtheria toxin, and in 1891 von Behring and Wernicke announced the discovery of diphtheria antitoxin.

Further progress in the control of diphtheria was made when Schick in 1913 described the intradermal toxin reaction for the determination of individual immunity and susceptibility to diphtheria. This test was shown to have great practical value by Park and Zingher, who applied it on an extensive scale in the schools of New York City. In 1913 von Behring recommended the use of toxin-antitoxin mixtures for active immunization against diphtheria. This form of immunization has been employed on a broad scale in this country and abroad.

Incidence.—Diphtheria is an endemic disease in larger centers of population. It becomes epidemic, especially in the colder seasons of the year. In rural sections and small communities, where the proportion of susceptible individuals is very large, the disease may become quite virulent.

Etiology.—Infection by direct contact occurs in the great majority of cases. The diphtheria bacilli are present in the nasopharyngeal discharges of patients and carriers, and the infection is spread by kissing, coughing, and sneezing ("droplet infection"). Indirectly the infection is spread by toys, pencils, spoons, dishes, feeding bottles, and drinking cups. Out-

breaks of diphtheria have been traced to contaminated milk, which in most cases has been infected by carriers at the dairies rather than by primary disease of the udders of cows.

Membranous infections have been described in cats, fowl, and pigeons, but are not identical with the disease found in human beings. Infection of horses caused by a diphtheria-like organism has been described by Cobbet and more recently by Minett.

Among *predisposing causes* are *age* and *sex*. Over 64 per cent. of all cases of diphtheria occur in patients less than five years of age, and over 80 per cent. in children under the age of ten. By means of the Schick test it has been demonstrated that fully 85 to 95 per cent. of children are susceptible to diphtheria at the end of the first year of life. Females are somewhat more frequently affected than males, and their greater susceptibility has also been demonstrated by the Schick test.

Infections and *trauma*, such as operations on the nose and tonsils, lower the local resistance of the mucous membrane of the nose and throat, and favor the development of diphtheria.

The children of the more *well-to-do classes* and those living in small communities are much more susceptible than those of the poorer classes who live in closely crowded sections of cities, where frequent contact exposure to infection brings about the so-called *"natural immunity"* to diphtheria. Among nurses from small towns and rural sections who have recently come into training-schools 40 to 80 per cent. react positively to the Schick test.

It is striking that all the children of a family usually react similarly to this test. In certain families the children tend to develop a "natural immunity" at the age of two or three years; while in others the susceptibility persists for a number of years.

Individuals of certain *races* have also been found to develop immunity to diphtheria more readily than those of other races. The highest percentage of negative reactions in the tests made in the New York City schools was among the children of Italian parents.

Bacteriology.—The *Bacillus diphtheriæ* is a rod-shaped organism which in cultures shows considerable variations in size and shape. As a rule, the bacilli lie parallel. They are straight or slightly curved, and when stained with Löffler's methylene-blue assume a granular, barred, or solid appearance. The granular form with dark-staining polar bodies at the ends is very characteristic. The bacillus is Gram-positive. Organisms that are identical in appearance but do not produce toxin and are, therefore, non-virulent are frequently found in nose and throat cultures. The toxicity test in the guinea-pig is the only means by which the non-virulent can be distinguished from the virulent strains.

Smears made directly from diphtheria lesions may contain very suspicious bacilli, but a definite diagnosis can only be made by culture. The bacillus grows best and in most characteristic form on Löffler's medium, which is a mixture of glucose, bouillon, and blood-serum. On ordinary culture-media the growth is less typical.

The diphtheria bacillus produces a soluble toxin which is destroyed when heated to 75° C. for ten minutes. The toxin passes through Berkefeld and porcelain filters and when injected into susceptible animals causes death in the same manner as when the bacilli have been injected.

Diphtheria-like bacilli, frequently termed *pseudodiphtheria bacilli*, have been described. They comprise a heterogeneous group, some of which are pathogenic, others harmless. They are distinguished from true diphtheria bacilli by morphology, culture characteristics, and certain sugar fermentation reactions. The *Bacillus xerosis*, which resembles the barred type of the diphtheria bacillus, has been found in some forms of conjunctivitis. The *Bacillus Hoffmanni*, which is non-virulent, is frequently found in the nasopharyngeal passages. It is a short, straight, oval bacillus with rounded ends and one median, lightly stained, transverse septum. Some of the larger forms resemble the diphtheria bacillus.

Morbid Anatomy.—Distribution of the Membranes.—In a series of 251 cases reported by Mallory a definite membrane, which varied in extent and location, was observed in 148 patients. The distribution of this membrane was as follows:

Location.	No. of cases.
Larynx	86
Tonsils	74
Trachea	73
Epiglottis	67
Bronchi	44
Mucous membranes of nares	43
Soft palate, including the uvula	15
Esophagus	12
Tongue	9
Stomach	5
Duodenum	1
Vagina	2
Skin of the ear	1
Conjunctiva	1

It was confined to the tonsils alone in 9 cases, to the larynx in 5, to the trachea in 3, to the pharynx in 2, to the epiglottis in 2, to the soft palate in 1, and to the mucous membrane of the nares in 1. In all other cases several structures were involved.

The lesions of diphtheria are local and general or systemic. The former are due to the action of the toxin on the tissue cells at the site of infection; the latter to the toxin which is absorbed through the blood and lymph channels and acts upon the tissues in various parts of the body.

Local Lesions.—The local lesions are in all situations essentially of the same character, namely, degenerative changes in the epithelial cells and an abundant fibrinous exudation from the blood-vessels into the underlying tissues. As a result there is formed on the epithelial surface a membrane which is so striking and characteristic a feature that the disease has been named from it. Sometimes when the epithelial cells are necrotic and the destructive process involves the underlying tissue, the membrane formation extends into the submucosa. The diphtheria bacilli are present on the surface and in the superficial parts of the membrane, but in the deeper layers of the false membrane and in the mucous membrane itself they are few or absent.

Macroscopically the membrane varies in appearance and consistency. The color is usually gray, but it may be yellowish green or even reddish black because of extravasated blood. When essentially fibrinous the membrane retains its form and may be discharged as a complete cast of the part affected. When it contains less fibrin it may be soft and friable.

Systemic Lesions.—The systemic lesions involve the various viscera, the musculature of the heart and blood-vessels, and the nerve-fibers.

The heart muscle undergoes fatty degeneration in more than half of the fatal cases. This is always more marked in the vicinity of the endocardium. There is also an interstitial myocarditis which may lead to extensive formation of fibrous tissue.

The kidneys show acute degeneration of the epithelium, which leads to cloudy swelling of the cortex. Interstitial changes are also fairly common. In the more severe cases the kidneys are greatly enlarged.

The spleen is swollen and congested, and the Malpighian bodies prominent.

Bronchopneumonia is frequently present in infants and young children, and is a complication in nearly all the fatal cases.

Degenerative changes occur in the peripheral nerves. The medullary sheath undergoes fatty degeneration and is broken up into globules. The axis-cylinder is also involved. Both the sensory and motor fibers may be affected. Degeneration of the cells of the anterior horn has also been described, a few observers claiming that the peripheral nerve changes are secondary. The work of most observers, however, goes to prove that the condition is purely peripheral, especially in the less severe cases of diphtheritic paralysis.

Pseudomembranous Inflammations in Other Diseases.—In more than one-third of scarlet fever patients a membranous exudate covers the tonsils, fauces, and nasal mucous membrane. In most of these the hemolytic streptococcus is the causative agent.

Similar pseudomembranous inflammations have also been found in other infectious diseases, such as measles, whooping-cough, and typhoid fever. In measles the croup characteristic of the early stages of the disease often suggests the possibility of laryngeal diphtheria.

Pseudomembranous inflammations of the throat are also caused by syphilis, Vincent's angina, and infections of the mouth by the leptothrix and the yeast organisms.

Symptoms.—The period of incubation is from two to five days.

The *initial symptoms* may be very slight. The patient complains of a little soreness of the throat; the temperature is slightly elevated, varying between 100° and 103° F., but the subject is often not ill enough to remain in bed. The local lesions begin most frequently in the pharynx, affecting especially the tonsils, the larynx, the nose, or the nasopharyngeal mucous membrane.

Pharyngeal Diphtheria.—In the early stages of pharyngeal diphtheria congestion of the fauces and tonsils is followed by the formation of a grayish translucent film, which later is rendered opaque by the deposition of a grayish-white fibrinous deposit on the tonsil. The membrane may be confined to the tonsil or may spread to the uvula, the pillars, and even to the soft palate. The lesion may extend to the posterior pharyngeal wall. On the third or fourth day the membrane is quite thick and may cover a considerable part of the fauces. In most cases it is sharply defined. There is some edema and swelling of the soft parts, especially of the fauces and uvula. The membrane can only be pulled off with difficulty and leaves behind it a bleeding raw surface which is soon covered by a fresh exudate. The cervical lymph-glands behind the jaw are enlarged and tender. The

membrane persists for six or seven days when untreated, but if antitoxin is administered it disappears sooner.

In mild or moderately severe cases the fever continues for five or six days; the pulse varies between 100 and 120. The white blood-count rises to between 15,000 and 25,000. With the disappearance of the membrane the local and constitutional symptoms also leave, the swelling of the lymph-glands subsides, and swallowing becomes easy and natural.

In severe cases not influenced by the early administration of antitoxin the onset may be very much like that in mild cases, but the symptoms gradually increase in intensity until they reach their maximum on the fifth or sixth day. The membrane on the tonsil spreads to the pillars, uvula, and palate, and at times to the nasopharynx, larynx, and trachea. The color of the membrane changes to a dark, dirty gray, and there is an intensely fetid odor to the breath. The discharge of mucus from the nose and mouth may be profuse and associated with obstruction to nasal respiration. The cervical glands become greatly enlarged and edema of the surrounding cellular tissue causes the formation of an indurated tender mass below the angles of the jaw. The temperature may be normal or subnormal, the pulse is rapid and feeble, and the patient presents evidence of sepsis. Coma and death gradually supervene.

Septic diphtheria, in which the streptococcus plays an important secondary rôle, is characterized by extreme edema at the site of the lesion, a higher and more prolonged fever, and a greater tendency to the formation of a collar of matted glands around the neck. The nasal discharge is often profuse, and the disease is frequently complicated by involvement of the middle ears. The mortality is high.

A *hemorrhagic type* of diphtheria is occasionally seen. In these cases the toxemia is severe and there are small hemorrhages into the skin and bleeding from the mucous membranes. The prognosis is very serious, death usually occurring within a week.

There are certain *atypical forms of pharyngeal diphtheria* in which the presence of the diphtheria bacillus is the only diagnostic sign. A catarrhal angina without formation of a membrane has been described as the result of infection by the Klebs-Löffler bacillus. Other cases resemble typical follicular tonsillitis, in which the patches may remain discrete or may fuse rapidly into a pultaceous membrane.

Nasal diphtheria is of two distinct types. In one the clinical course is rather mild. There is a mucopurulent or sanious discharge from the nose and the nares may or may not be occupied by a membrane. If such a growth is present, however, it extends for only a short distance into the nasal cavity. The cervical lymph-glands are not much enlarged and the constitutional symptoms may be slight or absent. The second type of the disease, which begins in the posterior part of the nasal cavity and in the nasopharyngeal vault, is often one of the most malignant forms. The membrane may not be visible at first, but within two or three days the palate and uvula become rigid and edematous, the membrane appears around the uvula, and spreads forward along the hard palate even as far as the teeth. It covers the nostrils and is seen on the posterior pharyngeal wall. The glands of the neck are greatly enlarged because of the rich lymphatic supply in this region. The constitutional symptoms are pronounced. This type of diphtheria has a grave prognosis, both as regards immediate

recovery and the possibility of the development of late cardiac and paralytic complications.

Laryngeal diphtheria is also called membranous croup. The symptoms begin with a harsh croupy cough which persists for a day or two. The patient then becomes suddenly worse, the respiration more difficult, and the dyspnea continuous. There is retraction of the supra- and infraclavicular spaces, the suprasternal fossa, the lower intercostal spaces, and the epigastrium. As aëration of the blood diminishes there is an increasing cyanosis of the lips and finger-tips; and the face, at first pale, becomes bluish. The respiration rate increases and there is a loud stridor with inspiration and expiration. The patient becomes very restless; the skin is cold and clammy; the temperature gradually rises; and the subject passes slowly into a state of stupor and coma. Convulsions may precede death. Great improvement may follow the dislodgment of the membrane by vomiting and coughing, although in many cases it forms again.

In the less severe cases the dyspnea and cyanosis are not so marked and the symptoms closely resemble those of moderately severe catarrhal laryngitis. Many cases of laryngeal diphtheria are complicated by bronchopneumonia.

The partial closing of a larger bronchus during tracheobronchial diphtheria by exudate produces definite local signs over the area of the lung supplied by the impaired bronchus. The condition may be bilateral, unilateral, or limited to one lobe or part of a lobe. Emphysema-like changes develop in the lung tissues. On percussion there is hyperresonance, and on auscultation the respiratory sounds are distant, the respiration being prolonged and low pitched in comparison with the rather harsh respiratory murmur over the unaffected lung.

Diphtheria of Other Parts.—Diphtheria of the *conjunctiva* occurs occasionally as a primary disease. It may be quite severe and cause various deformities of the conjunctiva. *Corneal ulceration* may occur and may greatly impair the sight.

Diphtheria of the *middle* and *external ear* may follow the extension of the disease from the nasopharynx.

Diphtheria of the *skin* may be seen in the more severe tonsillar forms in which the process extends to the lips and adjacent portions of the skin. *Wound diphtheria* has been described, but the diagnosis should be limited to those cases in which Klebs-Löffler bacilli are present in the cultures. *Pseudomembranous infections of wounds* are more frequently due to the streptococcus.

Diphtheria of the *vulva*, at times primary, more often secondary to infection from the nose and throat, is sometimes seen in females.

Complications and Sequelæ.—*Bronchopneumonia* is a frequent complication, especially of laryngeal diphtheria, and in the later stages of diphtheritic paralysis of the palate and pharynx. It is an inspiration pneumonia and is due either to difficulty in expulsion of the mucopus or to aspiration of particles of diphtheritic membrane or food.

Hemorrhage from the nose and throat is not uncommon in the more severe cases, when the membrane begins to separate from the underlying tissues.

Renal albuminuria and even *nephritis* develop in many of the severe cases.

Paralysis is one of the most important sequelæ. It is the result of a toxic neuritis due to the action of the diphtheria poison upon the myelin sheath and the axis-cylinder of the nerve.

Of the local paralyses, the most common involves the palate. Examination of the throat shows that the palate hangs flaccid and on being touched does not contract. The paralysis may be unilateral. There is a nasal character to the voice and swallowing is difficult because of return of liquids through the nose. When the constrictor muscles of the pharynx are also involved swallowing may be still further embarrassed.

Other forms of local paralysis involve the extrinsic and intrinsic muscles of the eye, and result in ptosis, strabismus, and loss of the power of accommodation. Involvement of the lower extremities is more frequent than that of the upper extremities. Occasionally the muscles of the neck and back, especially of the erector spinæ group, become paralyzed. Paralysis of the adductors of the larynx, which causes aphonia, and of the abductors, which leads to stridulous breathing and well-marked dyspnea, is not uncommon. Wolcott noted it forty-eight times in a series of 478 cases of paralysis. In severe generalized cases the sphincters become paralyzed. Among the most fatal of all forms of paralysis is that of the muscles of respiration. If the intercostals alone are affected there is no expansion of the chest on inspiration.

Cardiac Complications.—Involvement of the heart is a dangerous sequel of diphtheria. Irregularity of the heart has been frequently noted, but only a few patients suffer from serious cardiac symptoms. Rapid action of the heart with gallop rhythm and epigastric pain are the usual severe manifestations. The heart symptoms are generally noted in the second or third week of the disease, but dilatation may develop as late as the sixth or seventh week. The symptoms have been attributed to myocarditis and to degeneration of the vagus nerve.

Early heart failure is frequent in patients who have suffered from a fairly severe form of diphtheria, associated wtih profound toxemia. The symptoms are progressive. The pulse is rapid and feeble, the temperature normal or subnormal. The signs of cardiac dilatation lead generally to attacks of syncope, during which death may occur. Cardiac failure may also be unexpected and quite sudden in the early or late stages when patients have not shown a marked toxemia at the outset. In such instances it is caused by undue exertion. The late cardiac failure of convalescence is due largely to changes in the vagus and is seen sometimes in patients suffering from diphtheritic paralysis in other parts of the body. The first sign is a sudden increase in the pulse rate, associated with vomiting, precordial and epigastric pain. This is followed by attacks of syncope, extreme pallor, labored irregular respiration, and abnormal temperature.

Diagnosis.—Prompt diagnosis of diphtheria is very important, as the efficacy of antitoxin treatment depends largely on its early administration. The clinical diagnosis should, therefore, be the deciding factor whenever a bacteriological diagnosis cannot be made, or when the result of the throat culture cannot be known for twenty-four hours or more. The *age* of the patient is important, for diphtheria occurs chiefly among young children, who seldom suffer from follicular tonsillitis. In such patients, if scarlet fever and thrush can be excluded, any visible patching of the throat must be regarded as suspicious, and in any case should be treated as diphtheria.

The *location of the membrane* is also of importance. Unilateral exudate on the tonsil and patches of membrane on the uvula, pillars of the fauces, and soft palate are strongly suggestive of diphtheria. The disease occurs frequently on both tonsils, but, as a rule, is more pronounced on one side. A *sanious nasal discharge* should also arouse suspicion. *Marked lesions* with only slight swelling and absence of general redness of the fauces are suggestive of diphtheria, although septic diphtheria may cause considerable inflammation. *Slight fever* is also very suspicious evidence, as ordinary follicular tonsillitis is usually accompanied by considerable fever. Absence of pain on swallowing is another characteristic feature of diphtheria.

Differential Diagnosis.—In *follicular tonsillitis* the patches of exudate in the follicles are usually discrete, but sometimes spread and form a pultaceous membrane which wipes off easily. The history of a negative reaction to the Schick test is of importance.

Quinsy is characterized by high temperature, marked inflammatory swelling, and one-sided enlargement of the tonsil and peritonsillar tissue.

Vincent's angina may closely resemble diphtheria. A small patch about the size of a finger-nail forms on the tonsil, the anterior pillar, the uvula, or palate. The grayish exudate is closely adherent to the underlying ulcerated surface. The absence of the characteristic fusiform bacilli and spirillæ in smears made directly from the lesion establish the diagnosis.

In *thrush*, small milk-white patches are seen on the palate, gums, and buccal mucous membrane. There is practically no surrounding inflammation.

To differentiate *scarlet fever*, the presence of a rash is of assistance unless the patient is seen on the third or fourth day after the eruption has disappeared. The strawberry tongue, the angry redness of the whole of the fauces, including the soft palate, the character of the exudate, which is soft and wipes off easily, also help in the diagnosis. The two diseases may coexist.

Laryngeal Diphtheria.—Croup in a young child should always arouse a suspicion of diphtheria, and unless there is direct evidence to the contrary (negative Schick test) or the absence of membrane on direct laryngoscopical examination, the patient should be treated with antitoxin at once. Of great significance in the clinical diagnosis of laryngeal diphtheria is the presence of small patches of exudate on the tonsils, palate, and posterior pharyngeal wall.

Simple laryngitis is distinguished with difficulty. A history of recurrent attacks of croup which come on suddenly at night help in the diagnosis.

Laryngismus stridulus is seldom seen in children over two years of age and is frequently associated with rickets and tetany. The patient is, as a rule, fairly comfortable between the laryngeal spasms.

Edema of the glottis is often a complication of an acute streptococcus laryngitis, and may closely resemble laryngeal diphtheria. The absence of membrane and the presence of edema on direct laryngoscopical examination are significant.

Enlargement of the thymus gland is seen in children under one year of age. Pressure with the finger above the thymus at the suprasternal notch causes a temporary amelioration of the symptoms.

Retropharyngeal abscess is excluded by examination of the posterior

wall of the pharynx with the finger. Fluctuation is recognized without difficulty.

Bacteriological diagnosis is established by making a culture on a tube of Löffler medium and examining it after eighteen to twenty-four hours for the characteristic Klebs-Löffler bacilli. Löffler's methylene-blue and such differential stains as Neisser's polar-body stain give satisfactory results.

The following directions for taking cultures are recommended by the New York City Department of Health:

"The patient should be placed in a good light, and, if a child, properly held. In cases where it is possible to get a good view of the throat, depress the tongue and rub the cotton swab gently, but freely, against any visible exudate, revolving the applicator between the fingers, so as to bring all portions of the swab in contact with the mucous membrane or exudate. In other cases, including those in which the exudate is confined to the larynx, pass the swab back as far as possible, avoiding the tongue, and rub it freely as described above against the mucous membrane of the pharynx and tonsils. Withdraw the cotton plug from the culture tube, holding it so that the portion withdrawn from the tube does not come in contact with the fingers or with any other substance. Insert the swab and rub it gently but thoroughly back and forth over the entire surface of the blood-serum. At least half a minute should be given to this operation, the applicator being revolved so as to bring all portions of the swab in contact with the surface of the blood-serum. Do not allow the swab to touch anything except the throat of the patient and the surface of the serum. Do not push the swab into the serum, nor break the surface in any way. Do not use tubes in which the serum is contaminated, liquefied, or dried up. Replace the swab in its own tube, plug both tubes, mark the culture tube with name of patient for identification with accompanying blank, which should be fully filled out, and return both tubes and blanks promptly to a supply station. Unsatisfactory cultures, exhibiting insufficient growth or contamination by foreign bacteria, usually result from failure to follow carefully the above directions."

It is important to remember that only moderate reliance can be placed upon a single negative culture from the pharynx in purely laryngeal cases. Individual tonsillar or nasal cultures may also be negative when subsequent cultures will prove positive. The first duty of the physician in a doubtful case is to administer antitoxin; after this he is at liberty to make a more accurate bacteriological diagnosis.

Prognosis.—The chief factor in the prognosis is the prompt administration of antitoxin. Before the discovery of antitoxin the mortality from diphtheria was about 40 per cent.; since its use this figure has been gradually reduced, and now varies between 5 and 10 per cent. A few hours, delay in the administration of antitoxin may make an enormous difference in the prognosis. Table 1, taken from Ker, is representative of many other series which various authors have reported. The rapid increase in the mortality is well shown and the importance of administering the antitoxin not later than the third day is clearly emphasized.

Other factors that influence the prognosis are the age of the patient, the mortality being highest during the first two years of life; the location of the membrane, the prognosis being more serious in the laryngeal and nasopharyngeal cases; and the toxic character of the disease as shown by great enlargement of the cervical glands, gangrenous appearance of the throat, and marked prostration.

Prophylaxis.—Prevention of the spread of diphtheria bacilli from the *patient* is accomplished by isolation of the patient and disinfection of everything contaminated. Spoons, knives, forks, and dishes should be set apart for special use. The patient must be kept isolated until two successive nose and throat cultures prove negative. These discharge cul-

tures should not be taken until the temperature has been normal for ten days. If the cultures are persistently positive and the patient has remained isolated for more than eight weeks, the virulence of the bacilli should be tested in the guinea-pig. If they are non-virulent, the patient can be released from quarantine; if they are virulent, however, the only effective treatment found so far is to remove the tonsils and adenoids, the main source of infection. *Normal carriers* of virulent bacilli must also be isolated until their cultures are negative. The treatment of carriers by the *x*-ray has recently been recommended, but its value has not yet been confirmed.

Children who have been exposed to infection should be *immunized* with prophylactic doses of 1000 units of antitoxin. Whenever the conditions warrant it a Schick test should be made first to determine the susceptibility of the individual. In institutions in which there has been no diphtheria for some time and the disease has suddenly broken out, it is prefer-

TABLE 1

Relation of Mortality in Diphtheria to Time of Administration of Antitoxin

Day of illness.	Number of patients.	Deaths.	Percentage of mortality.
First	329	5	1.52
Second	2269	77	3.39
Third	2407	165	6.85
Fourth	1612	176	10.91
Fifth	911	136	14.92
Sixth	416	54	12.98
Seventh	320	53	16.56
Later	327	50	15.29
Total	8591	716	8.33

able to apply the Schick test first and then inject with antitoxin only those who react positively. Toxin-antitoxin should not be given when the conditions are urgent and immediate protection is desired, as active immunity does not develop for several weeks. Throat cultures should be taken and, if positive, the individual should be isolated. In homes for infants and in foundling asylums in which diphtheria is more or less endemic, the situation is best controlled by immunizing with toxin-antitoxin all the children in the institution and also all new children as soon as possible after admission. In this way diphtheria has been practically eliminated from two large infant asylums in New York City where it was prevalent for years. The best time to protect the child population against diphtheria is during the first six years of life and, preferably, during the first two years.

The Schick test determines in an easy and convenient way whether individuals are susceptible or immune to diphtheria. It is a very simple and valuable clinical procedure if properly carried out.

The test is made by injecting a small amount of diluted diphtheria toxin intracutaneously on the flexor surface of the right forearm about 2 inches below the bend of the elbow. The actual amount of toxin injected is 1/40 M. L. D. in 0.2 c.c. of salt solution. If the test has been properly made a small whitish wheal-like elevation about the size of a large split pea appears. A control test with toxin which has been heated to 75° C. for ten minutes to destroy the soluble toxin is made on the left forearm. The control test has proved to be a distinct help in the accurate interpretation of the reaction. Suitable outfits for the test and control are obtainable. In these the toxin is in a capillary glass tube, which can be emptied by means of a small rubber bulb into a bottle containing 10 c.c. of sterile salt solution. While the material in the bottles keeps well at ice-box temperature, the diluted toxin does not keep well and should not be used after twenty-four hours.

Four different reactions may result from the test—a positive, a negative, a negative-pseudo, or a positive-combined reaction.

The *positive reaction* to the Schick test depends on the local irritant action of a minute quantity of diphtheria toxin and indicates that the individual is susceptible to diphtheria. This reaction is characteristically manifested by a circumscribed area of redness and slight infiltration, which measures from 1 to 2 cm. in diameter. The reaction appears in twenty-four to forty-eight hours, reaches its height in four days, and persists for seven to ten days. It gradually fades and gives place to superficial scaling and a persistent circumscribed area of brownish pigmentation. To the control test in which the toxin has been destroyed by heat there is no reaction.

A *negative reaction* indicates that the individual is immune and has at least 1/30 unit of antitoxin per cubic centimeter of serum. This amount is necessary to neutralize the test toxin and is also the amount required to protect the individual surely against diphtheria. The skin remains unchanged both at the site of the test and of the control.

The *negative-pseudoreaction* indicates that the individual is immune to diphtheria, but is hypersensitive to the autolyzed substance of the diphtheria bacillus and to the other proteins contained in both the test and control solutions. The reaction is of an anaphylactic character, appears within six to twelve hours, reaches its height in twenty-four to thirty-six hours, and disappears on the third or fourth day, leaving behind only a poorly defined pigmentation with little or no scaling. The reactions are *equal* on both forearms and fade equally.

The *positive-combined* reaction represents a combination of the positive and pseudoreactions. This reaction is seen in only 5 per cent. of susceptible persons, and may be identified by its clinical course. On the fourth or fifth day the positive reaction appears clearly on the right forearm, while the control reaction on the left forearm is merely a faded area of brownish pigmentation.

In children under six years of age the reactions, as a rule, are frankly either positive or negative. In older children and especially in adults as much as 30 or 40 per cent. of all reactions may be of the negative-pseudo type.

Tables 2 and 3 show the results of tests made by Zingher on children in the public schools and in the baby health stations of New York City.

TABLE 2

GROUP A: THE SCHICK TEST IN BABY HEALTH STATIONS AND PLAY GROUNDS (MANHATTAN AND THE BRONX)

Age.	Total number of children tested.	Schick positive reactions.	Schick negative reactions.	Percentage of Schick positive reactions.
6– 7 months	53	30	23	56.6
7– 8 months	41	26	15	63.4
8– 9 months	62	52	10	83.8
9–10 months	58	54	4	93.1
10–11 months	61	53	8	87.0
11–12 months	34	31	3	91.1
1– 3 years	1727	1438	289	83.2
4– 6 years	1328	779	549	58.6
7–10 years	903	330	573	36.5
11–14 years	235	53	182	22.5
Total	4502	2846	1656	63.2

TABLE 3

THE SCHICK TEST IN THE PUBLIC AND PAROCHIAL SCHOOLS OF NEW YORK (MANHATTAN AND THE BRONX)

Age, years.	Total number of children tested.	Schick positive reactions.	Schick negative reactions.	Percentage of Schick positive reactions.
5– 6	4,809	2,902	1,907	60.3
6– 7	13,754	6,944	6,810	50.4
7– 8	16,180	7,042	9,138	43.5
8– 9	17,126	6,278	10,848	36.6
9–10	18,065	5,825	12,240	32.2
10–11	18,057	5,308	12,749	29.3
11–12	17,994	5,075	12,919	28.2
12–13	16,258	4,327	11,931	26.6
13–14	14,138	3,271	10,867	23.1
14–15	9,650	1,906	7,744	19.7
15–16	4,861	869	3,992	17.8
16–17	369	68	301	18.4
Total	151,261	49,815	101,446	32.9

In suburban communities and in rural sections the percentage of susceptible children is very much higher than in the city, reaching 85 to 95 per cent. Ten to 20 per cent. of the adults in cities show positive Schick reactions; in smaller communities the proportion may reach 60 to 80 per cent. Repeated contact exposure to infection in crowded cities is an important factor in producing the so-called "natural immunity" to diphtheria.

TOXIN-ANTITOXIN IMMUNITY.—The mixtures of toxin-antitoxin at first used were slightly underneutralized and contained in each cubic centimeter 3 L+ doses of toxin and 3.5 units of antitoxin. These preparations caused a certain amount of local irritation and constitutional disturbance in 10 to 20 per cent. of the school children and in an even larger percentage of adults. Such reactions have been largely eliminated by using a diluted mixture of toxin-antitoxin which contains only 0.1 L+ dose of toxin per cubic centimeter. The 0.1 L+ mixture is also underneutralized, but contains only a fraction of the proteins that caused the disagreeable reactions when the 3 L+ mixtures were given. Three successive injections of 1 c.c. should be given at intervals of one week. The preparation is injected into the arm subcutaneously or, preferably, intramuscularly.

From 85 to 95 per cent. of those receiving three injections of toxin-antitoxin become immune. Active immunity after toxin-antitoxin develops rather slowly; many of the injected children do not react negatively to the Schick test until six to twelve weeks have elapsed. Once acquired, however, the immunity lasts many years, and may be permanent. The Schick retest should be made, as a rule, after six months. If still positive, a second series of toxin-antitoxin injections may be given. It has been found, however, that about half of these children who react positively will show a negative Schick reaction if retested a year later, even though they receive no further injections of toxin-antitoxin. This indicates a slow development of the active immunity. There are about 2 per cent. of individuals in whom it is difficult, even with several series of toxin-antitoxin injections, to produce sufficient antitoxin to obtain a negative Schick test.

Toxin-antitoxin is not a substitute for antitoxin, which gives an immediate passive protection against diphtheria.

It is most desirable that all young children between the ages of six months and six years should be immunized with the three doses of toxin-antitoxin. The preliminary Schick test may be omitted in this group, as fully 95 per cent. of children are susceptible to diphtheria when they reach the age of twelve months. Vital statistics also prove that over 60 per cent. of all cases and over 80 per cent. of all deaths from diphtheria occur in individuals less than five years of age. By immunizing all young children as soon as they approach the end of the first year of life a diphtheria-immune population could soon be produced and the disease practically stamped out.

Before the age of six months many babies are temporarily protected against diphtheria if their mothers are immune. The antitoxic antibodies are transmitted through the placenta from mother to offspring during intra-uterine life.

Adults, especially physicians, nurses, and hospital attendants, who are frequently exposed to diphtheria, should be given the Schick test, and, if found susceptible, should be immunized with toxin-antitoxin.

Recent work by Glenny and Hopkins, Ramon, and Zingher and Park has shown quite definitely that good immunity can be obtained with *diphtheria toxoid*—anatoxin, Ramon. This is prepared by adding to the toxin 0.3 to 0.4 per cent. formalin and then allowing the formalinized toxin to remain at incubator temperature for four or five weeks. The toxicity of the toxin is completely destroyed, but its combining properties for antitoxin and its immunizing value for human beings and for animals are retained. The dose is 0.5 to 1.0 c.c. repeated at intervals of seven days until three injections have been given. Ramon recommends two doses, the first 0.5 c.c., the second 1.0 c.c., the injections to be given three weeks apart. The best immunity results (95–98 per cent.), however, were obtained by the author with three doses of Ramon's toxoid (anatoxin). The amounts injected were 0.5, 0.5, and 1.0 c.c., at intervals of two weeks. It is probable that in most of the mixtures of toxin-antitoxin the slight amount of free or partially bound toxin and toxoid are the real immunizing agents.

Treatment.—General.—The patient should be kept in bed, and in the more severe cases even the *slightest exertion* should be forbidden. Milk is the main article of *diet*, but may be supplemented by broth and occasionally by a beaten egg. After the temperature has subsided the diet should be soft, consisting of milk, puddings, cereals, soft-boiled eggs, stewed fruit, and jellies. Difficulty in swallowing due to paralysis of the muscles of deglutition sometimes necessitates nasal feeding through a small catheter. This should be performed by a trained person, as otherwise aspiration into the larynx and bronchopneumonia may result.

Stimulants may be necessary in the very severe cases. Digitalis and

adrenalin are necessary in threatened cardiac failure. All forms of treatment are frequently disappointing after acute cardiac symptoms have once manifested themselves. The acute restlessness and the vomiting may be held in check by small doses of morphin and atropin. The patient must be kept in an absolutely recumbent position and requires careful nursing.

Antitoxin Treatment.—The greatest advance in the treatment of diphtheria has been the discovery of antitoxin. Its efficiency depends on the administration of a sufficient dose as soon as possible to prevent the action of the diphtheria toxin upon the heart and the nervous system. If treated with antitoxin within the first twenty-four hours of the disease, nearly every patient can be saved. Delay of two, three, or four days may mean irreparable injury to vital organs by the absorbed toxin which cannot be neutralized by subsequent administration of even enormous doses of antitoxin.

The earlier the remedy is administered, the more certain and rapid is the effect. In illness of any severity which is suspected of being diphtheria, and in croup, it is far better to administer the remedy at once, making a culture at the same time, than to delay the treatment until a diagnosis has been made by bacteriological examination. The first injection should be large enough to control the disease. One large dose given early is far more efficacious than the same amount in divided doses. Very sick patients, those who have only received antitoxin after a delay, or patients in whom the disease is progressive because of an insufficient first dose, should be given a large intravenous injection whenever feasible. In this way the full value of antitoxin is obtained at once; the absorption from the subcutaneous injection is so slow that many hours must elapse before any great amount of antitoxin finds its way into the general circulation. For intravenous purposes the antitoxin must be warmed to body temperature and given very gradually.

The antitoxic serum obtainable at the present time is a refined and concentrated preparation made by precipitation of the antitoxic or "soluble" globulin from the sera of immunized horses. By this process a considerable portion of the serum protein and other serum constituents are eliminated, while the antitoxic properties are retained and concentrated. Rashes and other deleterious effects sometimes caused by the injections of serum are less apt to follow the administration of the concentrated antitoxin.

Table 4 gives the doses recommended by the New York City Department of Health:

TABLE 4

Amount of Antitoxin Required in the Treatment of a Case

	Mild cases.	Moderate.	Severe.[1]	Malignant.[1]
Infants, 10 to 30 pounds in weight (under two years of age).	2000 units to 3000 units	3000 units to 5000 units	5000 units to 10,000 units	7500 units to 10,000 units
Children, 30 to 90 pounds in weight (under fifteen years of age).	3000 units to 4000 units	4000 units to 10,000 units	10,000 units to 15,000 units	10,000 units to 20,000 units
Adults, 90 pounds and over in weight.	3000 units to 5000 units	5000 units to 10,000 units	10,000 units to 20,000 units	20,000 units to 40,000 units

[1] When given intravenously one-half the amounts stated.

Cases of laryngeal diphtheria, moderate cases seen late at the time of the first injection, and cases of diphtheria occurring as a complication of the exanthemata should be classified and treated as "severe" cases.

In all cases a single dose of the proper amount, as indicated in the schedule, is recommended.

It is recommended that the methods of administration be as follows:

Mild cases—Subcutaneous or intramuscular.
Moderate cases—Intramuscular or subcutaneous.
Severe cases—Intravenous or intramuscular.
Malignant cases—Intravenous.

The average case of diphtheria is best treated by intramuscular injection in the gluteal region, the posterior axillary fold, the infrascapular region, or the outer aspect of the thigh.

The Effect of the Antitoxin.—The injection of antitoxin is usually followed by a striking improvement in the symptoms even when administered as late as the third day of the disease; after this time its value diminishes rapidly. Within twenty-four hours after the injection of the antitoxin the membrane stops spreading, begins to soften and loosen. The swelling of the mucous membrane subsides. In some cases the membrane apparently spreads and the alarmed physician is tempted to give a second dose of antitoxin. What has really happened, however, is that the area of mucous membrane which corresponds to the extending portion of false membrane has been injured by the toxin previous to the injection of the antitoxin, and the appearance of the fibrinous exudate is simply the later manifestation of the damage that has already taken place.

The constitutional symptoms are also strikingly improved, as is manifested by a fall in temperature and a favorable change in the character of the pulse and nervous symptoms.

Serum Sickness and Anaphylaxis.—*Sudden death* following the injection of antitoxin has been reported in a few instances. This complication, according to Park, occurs about once in 70,000 injections, and is more frequent after intravenous than after subcutaneous or intramuscular injections. It is not a true anaphylactic reaction as is generally seen after a primary injection. Such sudden deaths have been reported, as a rule, in patients suffering from bronchial asthma or status lymphaticus.

Pirquet and Schick have described two types of *serum disease* which follow the injections of foreign sera: an accelerated form which develops thirty minutes or several hours after the injection; and a late form, usually designated as serum sickness, which develops eight to fifteen days later.

The accelerated form occurs in only a small proportion of injected individuals, and is characterized by intense dyspnea, cyanosis, prostration, and a marked urticarial rash. These symptoms, in a mild, moderate, or severe form, may follow the injection of antitoxin whether it be subcutaneous, intramuscular, or intravenous.

Serum sickness proper develops in 10 per cent. of injected individuals. The first symptom is a more or less extensive urticarial rash (morbilliform, erythematous, and scarlatiniform rashes have also been described) associated with itching of the skin, elevation of temperature, and swelling and tenderness of some of the joints. Localized edema of the mucous membrane of the epiglottis and of the larynx, with puffiness of the eyelids and even slight albuminuria, have been noted. All these symptoms, with the exception of the urticarial rash, are rare when the concentrated and refined antitoxin has been used.

In patients with bronchial asthma it is advisable to avoid intravenous injection and to give the antitoxin in very small doses (beginning with 0.1 c.c.) which are repeated every twenty minutes. Antitoxin obtained from goats, if procurable, should be used by preference.

A *preliminary intradermal test* may be made for hypersensitiveness to horse-serum, when patients give a suspicious history of asthma or have had antitoxin previously, by injecting them with a small amount. One-fortieth of 1 c.c. of the antitoxin diluted 1 : 100 with sterile salt solution is injected intradermally on the flexor surface of the forearm. Individuals who are unusually susceptible to horse-serum will show within five to ten minutes at the site of the test, a large urticarial wheal surrounded by a distinct areola. In such cases it is advisable to inject the antitoxin in minute doses (0.1 c.c.) every twenty minutes until the total amount has been administered. Intravenous injections should be avoided.

Besredka has recommended desensitization by injecting subcutaneously 0.5 c.c. of antitoxin, to be followed after four hours by the therapeutic dose. This method, however, has not always proved satisfactory and causes delay.

Adrenalin and atropin to be of value must be used before the injection of antitoxin or at the first intimation of symptoms. After the symptoms have fully manifested themselves these drugs are of only limited value.

Local treatment is used to a much less extent since the introduction of antitoxin. Gargles of normal saline or Dobell's solution may be used for their cleansing effect. In the septic nasal type of diphtheria with profuse discharge gentle syringing with normal salt solution every three hours is advisable. Force should be avoided.

Local applications to the neck relieve pain and tension from the swollen cervical lymph-glands.

Paralysis.—For paralysis very little can be accomplished by any form of treatment. Antitoxin should not be given, as it has no value at this late stage of the disease. Strychnin may be administered in small doses. If the swallowing muscles are paralyzed, careful nasal feeding in young children is important. Gentle massage is useful for paralysis of the limbs. As a rule, postdiphtheritic paralysis is of a transient character, but it may precede late cardiac failure, and for this reason the patients should be kept perfectly quiet.

Laryngeal Diphtheria.—This disease requires the early administration of a sufficient dose of antitoxin, preferably by vein. To alleviate the dyspnea and relax the spasm, inhalation of steam is helpful, especially when it is carried out under a closed tent. Small doses of calomel, not to exceed 10 grains, may also be vaporized every four hours.

Increasing dyspnea, retraction of the soft parts of the chest, slight cyanosis, restlessness, and a rising temperature indicate the necessity of intubation. Tracheotomy is less frequently performed now. As a rule, intubated patients are better off in a hospital where they can be under constant observation.

Intubation.—This was introduced in 1885 by Dr. Joseph O'Dwyer, of New York City. The necessary instruments consist of a set of metal tubes lined with hard rubber, an introducer, an extractor, and a metal disk gage for determining the proper caliber of the tube.

During the operation the patient, wrapped in a blanket or sheet, lies upon his back on the table, the head being steadied by an assistant. The tube is attached to the intubator, the mouth-gag introduced into the left angle of the mouth and opened as far as possible. The operator stands at the right side of the patient. The left index-finger, which serves as a guide, is passed back into the pharynx, then brought forward until the nodule of the cricoid cartilage is felt in front of the epiglottis. The tube is passed along the palmar surface of the index-finger and is guided by it over the epiglottis into the opening of the glottis. The tube is then pushed off the intubator by a thumb pin attached to the handle.

The loop of silk which is passed through the head of the tube before it is introduced is not removed until the operator has ascertained that the tube is in place and the dyspnea relieved. It is then cut through and pulled out. Accidental removal of the tube from the larynx is prevented by re-introducing the index-finger and pressing down upon the head of the tube. Some operators prefer to leave the silk loop in place and attach it to the cheek or back of the ear by means of a small piece of adhesive plaster.

The false membrane, especially when loose, is sometimes pushed down by the tube and obstructs the larynx below it. This serious accident calls for tracheotomy or, preferably, for intratracheal suction when an outfit for that purpose is available.

The tube is left in place for from one to six days. The feeding is important. Nursing, as a rule, is not interfered with. Older children when being fed should be in a recumbent position, the head held slightly lower than the body.

The tube is removed by means of the extubator. The patient is in the same position as for intubation. The left index-finger of the operator is placed upon the head of the tube, which is steadied externally by the thumb of the same hand. The beak of the extubator is introduced within the opening of the tube, its jaws are then separated by pressure upon the lever on the handle, and the instrument holding the tube withdrawn. After removal of the tube the operator waits to see if the dyspnea returns.

Food should be withheld for two hours before the operation to avoid vomiting and introduction of food into the larynx. If the dyspnea does not return during the next three to four hours, it is possible that the tube will no longer be required.

About 1 per cent. of the intubated patients require prolonged intubation. The majority of patients will be able to do without the tube in a few weeks, but some develop a chronic inflammatory condition of the subglottic region of the larynx and require prolonged intubation and subsequent treatment by larger and larger tubes to produce increasing intralaryngeal pressure.

Tracheotomy.—For tracheotomy the patient is wrapped in a blanket and a sand-bag or rolled-up sheet is placed under the shoulders. Local anesthesia is used. The head is held firmly by an assistant who is instructed to keep the chin always in the midline. Steadying the larynx between the thumb and middle fingers of the left hand with the forefinger resting on the lower margin of the cricoid, a skin incision about $1\frac{1}{2}$ inches is made in the midline from the tip of the finger downward. The larynx continues to be held steady and the lower edge of the cricoid is again felt in the wound. If time permits, the trachea is now exposed by dissection, and the first two or three tracheal rings divided; but if haste is necessary, the trachea is opened by a bold plunge with the scalpel. The wound is held open by retractors and any visible membrane removed with forceps. The tracheotomy tube is then inserted and fastened by tapes passed through the opening in the shield and around the neck. A light gauze dressing is placed over the shield and the air in the room kept warm and moist by a croup-kettle near the bed. The inner tube should be removed and cleaned from time to time. Food is administered through a nasal tube. The tracheotomy tube must be left in for three to seven days before the patient can dispense with it; rarely, for months before the patient can breathe normally.

Treatment by Suction.—Suction of the membrane with the aid of direct laryngoscopy in cases of laryngeal and tracheobronchial diphtheria has been recommended by Lynah, Gover, and Hardman. For this a suction pump, laryngoscope, and a long metal aspiration tube are required. The operation is carried out at the Willard Parker Hospital in New York City as a routine in cases in which the membrane is loose and there is not too much edema of the mucous membrane. It is of great value in certain cases, but should be attempted only by one experienced in direct laryngoscopy who is quite capable of performing a rapid intubation or tracheotomy should the emergency arise.

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TETANUS

Definition.—Tetanus is an infectious disease caused by the *Bacillus tetani* (Nicolaier, 1884; Kitasato, 1889), and characterized by painful tonic spasms of the muscles, with acute exacerbations. The muscles of mastication, the masseters and pterygoids, are most commonly involved. Symptoms develop following the introduction of the bacilli as spores into a wound.

Incidence.—The disease, which was known to Hippocrates and earlier

writers, occurs in any part of the world where the soil is infected by animal or human excreta. In the registration area of the United States 1488 individuals, of whom 330 were infants less than one year of age, died from tetanus during 1922. Between March, 1916 and November, 1923 the Los Angeles General Hospital admitted a total of 100,000 patients. Of this number, 72, or one in every 1400, had tetanus. The disease is more common and more severe in tropical countries than in the United States.

Before the introduction of prophylactic measures the incidence always increased during war. Among the British wounded during the early part of the World War 15 to 32 of each 1000 developed tetanus. After injection of the antitoxin (Behring and Kitasato, 1890) became routine, however, never more than 2 or 3 per 1000 had the disease, and in many organizations the incidence was as low as 1 per 1000 (Bruce). The American troops were even more fortunate, in that all the wounded were injected with antitoxin throughout their service. Of the 224,089 wounded, only 36, or 0.16 per 1000, developed tetanus. This is the lowest incidence ever recorded during warfare.

Etiology.—Tetanus usually follows an injury. The type of wound responsible for the infection may be of an apparently trifling character. In many cases so-called clean, punctured or perforated wounds become infected, possibly because they receive less careful first-aid treatment than those which seem more dangerous. *Lacerated or punctured wounds of the hands or feet, which are caused by contaminated splinters or nails, are a common source of trouble.* Blank cartridge wounds are particularly liable to infection. In our series of 72 cases of tetanus the infection also originated in compound fractures; in the wound resulting from operation for gangrenous appendicitis; in blisters on the feet; in stitches with infected catgut (one instance); in the bite of a rabbit on the hand; in a bed-sore on the buttock which was probably contaminated by fecal discharges; and in the umbilical cord of an infant.

Bacteriology.—Tetanus bacilli are slender, slightly motile rods from 2 to 5 micra in length and 0.3 to 0.8 micra in breadth. Five or six different types have been isolated. They usually grow singly, and by producing a spore at the end acquire a drumstick appearance. They occur in earth, garden mold, manure, and putrefying liquids; they are normally found in the intestines of many ruminants, horses, and herbivora, as well as in the dejecta of healthy men. Bauer and Meyer found 24.1 per cent. of 530 specimens of human stools contained tetanus spores. The bacilli may contaminate vaccines, catgut, and commercial gelatins. They grow best under anaërobic conditions in alkaline broth, or on agar containing 1.5 per cent. glucose. The presence of sterile fresh tissue in the medium facilitates growth. Pyogenic organisms are also believed to favor development of the tetanus bacilli, especially when they occur in devitalized tissue contaminated with other anaërobic bacteria, such as the bacilli of gas gangrene. The bacilli readily perpetuate themselves outside the body, inasmuch as the spores are extremely resistant to the methods commonly employed to kill pathogenic bacteria, and may be destroyed only by extreme heat (boiling fifteen minutes at 15 pounds pressure or by superheated steam). The bacilli are stained by all ordinary dyes and by Gram's method; the spores, by the usual methods.

The toxin produced by *Bacillus tetani* is one of the most powerful sol-

uble poisons known; the dose fatal to man is 0.22 mgm. or about 1/300 grain. Rabbits and dogs are less susceptible to its action than most other animals; ducks and chickens are immune. The production of toxin begins as soon as the bacilli multiply, and is not necessarily restricted to the area of the wound, since the organisms may be transported from the point of injury to other parts of the body by phagocytes. The harmful action of tetanus toxin is due to its affinity for the central nervous system. Various theories have been advanced as to the manner in which it reaches the central nervous system. It may ascend to the spinal motor ganglia along the axis-cylinders or the lymphatics of the nerves supplying the infected area, or by being absorbed from the blood by the motor nerve end-plates in the muscles. It also attacks the sensory nerves.

Morbid Anatomy.—Except for the parenchymatous degeneration (cloudy swelling) incidental to any acute overwhelming toxemia, few and insignificant lesions are produced in the spinal cord, brain, muscles, or nerves by the action of the tetanus poison, even in fatal cases. Occasionally perivascular exudations and granular changes in the nerve-cells have been noted. The initial point of infection is often small and innocent in appearance, or it may not even be evident. In some instances the nerves near the wound may be injured, reddened, or swollen. The organs show only a general and moderate congestion. Few bacilli are demonstrable at the point of infection, and bacilli have only rarely been found in the blood or viscera.

Symptoms.—Incubation Period.—The incubation is the time required for the toxin to travel along the nerves to the centers; or it may be defined as the time elapsing between the infection with tetanus bacilli and the development of the first symptoms. In man this varies from five to seven days in acute cases, or from four to five weeks in chronic cases. In 56 of our cases the disease developed on the eleventh day. The incubation period is greatly prolonged if the antitetanic serum is administered.

Types of Tetanus.—There are several types of tetanus, including traumatic tetanus; postoperative tetanus (especially following peritoneal operations); visceral tetanus (described by the French); tetanus neonatorum, much less common since the discovery of the bacillus and the proper treatment of the umbilical cord; cephalic tetanus, which may follow a wound in the head; idiopathic tetanus, in which no portal of entry can be found; and localized tetanus. With the exception of the latter all are characterized by similar symptoms, although there is some distinguishing peculiarity.

Premonitory Symptoms.—These are induced by the hyperirritability of the nervous system, and usually consist of restlessness and irritability, slight stiffness of the neck, a sensation of tightness of the jaws, or difficulty in mastication or in swallowing. The patient may attribute the latter to sore throat. Stiffness of the arms or legs, headache, chilliness, and slight fever have also been observed. The importance of recognizing these premonitory symptoms which appear a few days after infection is great, as they are rapidly followed by the more characteristic and serious manifestations. In children the first symptom may be a general convulsion which recurs frequently.

Later Symptoms.—As the symptoms progress the neck usually becomes rigid, and the sensation of stiffness in the jaws is replaced by actual difficulty in opening them (trismus), a condition which is rendered more marked

by reflex stimulation when attempts to eat or drink are made. The face assumes a characteristic expression, the so-called sardonic smile (*risus sardonicus*), which results from spasm of the facial muscles and the involuntary raising of the eyebrows. The abdominal and lumbar muscles early assume a general board-like rigidity which may lead to opisthotonos. This abdominal rigidity has occasionally led to errors in diagnosis.

The painful convulsions and the rigid locking of the jaws are the most characteristic features of general tetanus. The convulsions are precipitated by noise, by jarring the bed, and by handling the patient. Profuse sweating accompanies them, and the vise-like constriction of the chest muscles renders the patient unable to cry out. Dysphagia may arise and interfere seriously with nutrition. Spasms may be so severe as to tear the muscles and cause hemorrhage. Cyanosis and asphyxia may result from spasm of the diaphragm or glottis. Urethral spasm is not unusual and leads to difficulty in micturition. Constipation is fairly constant. The pulse and respiration rates increase. The temperature commonly rises to 101° or 102° F. There is moderate leukocytosis, the white cell count rising to between 12,000 and 15,000. The highest count in uncomplicated tetanus in our series of cases was 17,600. The number of polynuclear cells may be increased to from 70 to 90 per cent. The spinal fluid is usually under increased pressure. Before injection of antitoxin it contains the normal number of cells, and, as a rule, is free from globulin except in patients with coexistent cerebrospinal syphilis. After the injection of antitoxin into the spinal canal, however, the cell count rises and globulin appears, owing to the meningeal irritation produced by the serum.

If treatment is ineffectual, death usually occurs on the third or fourth day of the disease as the result of asphyxia or of circulatory failure during a convulsion. Bronchopneumonia, which may be associated with hyperpyrexia, may prove fatal after eight or ten days.

Local Tetanus.—If the quantity of antitoxin injected as a prophylactic at the time of injury is insufficient to give full protection, the muscles around the wound become rigid and spastic. This condition is known as local tetanus, and is caused by the action of the toxin on the spinal motor nerve-cells which supply the muscles affected. For some unknown reason the toxin, which travels along the nerves, becomes localized in the cord. This "local tetanus" may develop weeks or months after an operation or injury, and is most frequently associated with chronic infection of bone. It is relatively rare.

The symptoms are pain and local increase of reflexes; persistent tonic contracture of affected muscles; early rigidity, spasticity, or even twitching of muscles surrounding wounds. Local tetanus differs from other types in that the tonic contraction of the muscles first affected may persist for weeks or months after all other symptoms have subsided. It is less likely to be fatal than other types.

Differential Diagnosis.—Although tetanus may resemble several other pathological conditions, differentiation is comparatively easy. The history of exposure or injury is, of course, of prime importance. In doubtful cases cultures should be made from the pus of the wound. Strychnin poisoning, which at times closely simulates tetanus, rarely involves the muscles of the jaw, and those of the neck and trunk are relaxed between spasms. Tetany also differs definitely from tetanus in the localization of the muscles affected,

the rigid extension of the fingers with the thumbs drawn in toward the palms, the plantar flexion of the feet and toes, the absence of rigidity of the jaws and of the lumbar muscles, and its probable association with rickets in children. Epilepsy and hysteria have quite distinct characteristics. The mild spasms of the glottis and accessory throat muscles which may occur in throat infections, such as peritonsillar abscesses and cellulitis, are not accompanied by the fixation of the jaws, characteristic of tetanus, and may be differentiated by local examination. The early symptoms of meningitis are occasionally confusing.

Prognosis.—Tetanus is more fatal in children than in adults. Of the 15 children with tetanus who were treated in the Los Angeles General Hospital during 1922 and 1923, 10 died. Infection of the umbilicus of infants (tetanus neonatorum) is fatal in a large proportion of cases, but is less common since the discovery of the bacillus and the prophylactic treatment of the umbilicus. According to Osler, if the patient survives the tenth day he has an even chance, and with each succeeding day the prognosis improves. Favorable indications are late onset, localization of spasms to the muscles of the neck and jaw, and absence of fever. Delay in the recognition of tetanus and in treatment greatly increases the mortality.

Modern therapeutic methods have markedly reduced the formerly high death rate of 80 to 100 per cent. When the incubation period is between eight and fifteen days, and treatment is begun within twelve to eighteen hours after the onset of symptoms, the proportion of fatal cases should not exceed 25 to 30 per cent. If the incubation period is as short as three to five days, however, or if treatment is delayed after the first manifestation of the disease, approximately 50 to 60 per cent. of patients will die in spite of treatment.

The average time between the onset of symptoms and the beginning of treatment in one series of 23 patients was 2.9 days. Twelve of these patients died. This mortality rate (52 per cent.) corresponds closely with that of the group of 49 patients treated in the same hospital between 1916 and 1921, none of whom received a prophylactic dose of antitoxin. Twenty-six (53 per cent.) of these earlier cases proved fatal. Among the wounded British in the World War who were given no preventive treatment the death rate from tetanus was similar (53.3 per cent.—Bruce).

If trismus appears early and is complete within twenty-four hours after the onset of the disease, the outlook is less favorable than when the jaws become fixed more gradually. Approximately 60 to 70 per cent. of the patients with early complete trismus die, as compared with 30 per cent. of those whose symptoms develop more slowly. This difference may be explained by variations in the degree to which the toxin becomes fixed in the cells of the spinal cord. The less complete the fixation, the greater the possibility that antitoxin will neutralize toxin.

Prophylaxis.—It is a serious reflection upon the progress of medical practice that, despite the suspicious character of many wounds, physicians often neglect to administer antitoxin for prophylactic purposes. The fact that many patients are not seen by physicians prior to the onset of tetanus may partially explain the lack of suitable prophylaxis. All lacerated wounds should be seen by a surgeon, because primary excision and suture of the injured tissues may be necessary. During the World War the prophylactic administration of antitoxin and surgical care of lacerated

wounds led to a marked decrease in the incidence of tetanus. A dose of 1500 units of tetanus antitoxin should be administered within twenty-four hours after the infliction of blank cartridge wounds, or of penetrating or lacerated wounds upon the suspicion that they have been infected with dirt or dust. Since the cautery produces necrotic tissue favorable to the growth of anaërobic organisms it should not be used for penetrating wounds. For superficial injuries the application of 3 per cent. iodin in alcohol and a sterile bandage will suffice.

Treatment.—In the treatment of tetanus several distinct features require consideration: the general welfare of the patient must be carefully watched; the wound must be given suitable surgical attention; and, most important of all, the toxin produced by the *Bacillus tetani* must be neutralized. Seclusion, quiet, a darkened room—everything that tends to soothe the irritated nervous system—should be assured. Since the rate of metabolism is greatly increased by the muscular spasms, it is essential that the patient be kept quiet and relaxed by the use of sedative drugs to prevent exhaustion. Phenobarbital (luminal) may be given in 3- to 5-grain doses by mouth or rectum every three to six hours for this purpose; chlorbutanol (chloretone) by mouth in doses of 15 to 30 grains in dilute alcohol or whisky at similar intervals is likewise effective. If the patient is under the influence of other drugs, morphin should be used with caution. Its quieting effect is greatly prolonged when it is combined with chemically pure magnesium sulphate (morphin gr. $\frac{1}{8}$ to $\frac{1}{4}$ suspended in 2 c.c. of 25 per cent. $MgSO_4$ solution). Whenever this combination is used to control the convulsive seizures of tetanus, the respiration of the patient must be watched with great care. For control of the spasms Smith and Leighton have advised the subcutaneous injection of 1.2 to 2.0 c.c. of a 25 per cent. solution of purified magnesium sulphate for each 20 pounds of body weight four times in each twenty-four hours. One c.c. of the 25 per cent. solution for each 20 pounds of body weight may be injected intraspinally once in twenty-four hours. For spinal injection in children the dose should not exceed 0.3 to 0.5 c.c. to each 20 pounds of body weight. If respiratory distress follows the use of magnesium sulphate, the intravenous injection of 3 to 5 c.c. of a 5 per cent. calcium chlorid solution rapidly relieves the symptoms. A liberal diet, whenever possible, to maintain the bodily nutrition is also important. From 2000 to 4000 calories in liquid form may be given daily for a considerable period. To prevent dehydration fluids should be administered by mouth or rectum. If the patient cannot relax enough to open the jaws, food may be given through a tube of small caliber which is passed through the nares or between the teeth. The patient should be constantly attended by a nurse, since during the convulsive seizures there is danger of death from asphyxia or from paralysis of the respiratory center.

The wound responsible for the development of tetanus requires the attention of a surgeon. Although many physicians have believed that it is safer to abstain from surgical intervention after symptoms of tetanus have appeared, amputation of a lacerated member, such as a toe, may be advantageous in that it removes the focus of infection without great risk to the patient. Unhealed wounds should be incised under local anesthesia, explored for foreign bodies, and left open to the air; 5000 units of antitoxin should then be injected into the tissues about the injured region.

The most important part of the treatment of tetanus is, of course, the administration of the specific antitoxin which neutralizes the poison produced by *Bacillus tetani*. This should be given early, as its administration has often proved ineffective when undertaken too late. If given promptly when premonitory symptoms are noted, and in specific doses, it should prove effective. As the result of the work of Park and Nicoll in 1914 the general practice in this country has been to inject 3000 to 5000 units of antitoxin into the spinal canal, and 10,000 to 15,000 units intravenously as soon as possible after the appearance of symptoms; to follow this by a second intraspinal injection of 5000 units on the second day of the disease; and, in order to prolong the effect of the antitoxin for four or five days, to inject 10,000 to 15,000 units subcutaneously three or four days after the second intraspinal injection. Increasing experience, however, has demonstrated that larger doses of antitoxin are of even greater benefit. This impression is corroborated by recent statistics from Great Britain, which show that the death rate in a group of 214 patients who received more than 100,000 units of antitoxin was only 11.4 per cent. (Bruce). It must be kept in mind, however, that administration of quantities of antitoxin sufficient to prevent death is impossible in many severe acute cases. Continuation of the large daily doses after the third or fourth day is probably of little value. Doses for children are as large as for adults, since the purpose is to neutralize the toxin, to which children are more susceptible.

The effects of antitoxin seem to be more beneficial when it is administered according to the following plan:

First Day.—In order to desensitize the patient 1 c.c. is injected subcutaneously. If no anaphylactic symptoms, such as dyspnea, cyanosis, or marked increase of the pulse rate, result, 20,000 units of antitoxin are injected intravenously thirty minutes later. If symptoms of anaphylaxis develop, the injection should be discontinued at once, and not repeated for three hours. After this interval the patient will probably be desensitized by the serum injected in the first attempt, and can usually receive the full dose. Injection of 20,000 units intraspinally follows the intravenous injection.

Second and Third Days.—The intravenous and intraspinal injections of 20,000 units are repeated on the second and third days.

Since the antitoxic effect has greatly diminished by the seventh to the ninth day it has been found advisable to administer 10,000 units of antitoxin intramuscularly about the eighth day to prevent a recurrence of symptoms from dormant bacilli or spores.

In the administration of antitoxin the gravity method has proved most satisfactory. The barrel of a large glass syringe may be used as container. To this the needle is attached by about 15 inches of rubber tubing. As there are soluble toxic substances present in new rubber, all new tubing should be left in a 5 per cent. solution of sodium hydroxid for half an hour before it is sterilized.

For intravenous injection the most convenient needles are about $1\frac{1}{2}$ inches in length and 18 to 19 gage. The antitoxin should be diluted with an equal volume of isotonic sodium chlorid solution, and should be kept at body temperature throughout administration. The first 10 c.c. should be given at the rate of about 1 c.c. per minute. If for any reason intravenous injection is impracticable, antitoxin may be given intramuscularly.

Anesthesia, either general or local, is necessary for the intraspinal injection. General anesthesia is always advisable for children and for patients in opisthotonos because of danger of breaking the needle. Children take chloroform, as a rule, without deleterious effects. Unless the necessary manipulation tends to bring on convulsions, adults require only local anesthesia. After insertion of the needle from 10 to 25 c.c. of the spinal fluid is collected for the globulin test and cell count. Before injection the antitoxin should be heated to body temperature, but dilution is unnecessary. The antitoxin is allowed to flow into the spinal canal by gravity from the same container used for intravenous administration.

WILLARD J. STONE.

CEREBROSPINAL FEVER

(*Spotted Fever, Epidemic Cerebrospinal Meningitis, Meningococcus Meningitis*)

Definition.—Cerebrospinal fever is an infection with the *Diplococcus intracellularis* which occurs sporadically or in epidemics. It is characterized by primary local involvement of the nasopharynx or tonsils, secondary invasion of the general blood-stream, and metastatic inflammation of the meninges, and, more rarely, of other parts of the body.

History.—To Vieusseux, of Geneva, and to Danielson and Mann, of Manchester, Massachusetts, belongs the credit of the earliest and independent description of this disease in 1805 and 1806. In 1811 North, of New York, published the first monograph on the subject. To Jochmann in Germany and Flexner in the United States belongs the credit of establishing serum therapy.

Incidence.—Sporadic cases are almost always present in any large community. At irregular and infrequent intervals epidemics occur. These most often arise where individuals are crowded together in new or unsanitary surroundings, as in army camps, jails, and other institutions. Nevertheless, as in New York in 1905, epidemics may arise without peculiar circumstances.

Etiology.—The *Meningococcus* was identified as the cause of meningococcus meningitis by Weichselbaum in 1887. It is a Gram-negative diplococcus almost strictly parasitic for man and can be grown on artificial media only if animal protein is present. The chief toxin seems to be an endotoxin, and phagocytosis the most important factor in immunity. There are several varieties or types of the organism, each with more or less peculiar immunological properties. These are classified by Dopter as the normal or regular type, the parameningococcus, and the intermediate strains. English bacteriologists describe *four* immunological types. It is important to recognize that serum which is active against one type may be inert against another. Apparently the disease is almost solely transmitted by "droplet" infection from the mouth or nose of the carrier. Carriers are always present in a community and may be individuals suffering from the disease or in the incubation period, or chronic or casual carriers.

Morbid Anatomy.—During meningitis there is intense congestion, often with punctate hemorrhages in the dura. In its earliest stages the disease is revealed by congestion of the pia-arachnoid and choroid plexus with localized infiltrations of round and polymorphonuclear cells and erythrocytes. The exudate typical of the later period of the meningitis lies between the arachnoid and the pia mater; is composed of leukocytes, fibrin, meningococci, and red blood-cells, and may be thin and milky or lie in thick, greenish-yellow masses about the base, or distributed along the sulci of the cortex and throughout the ventricles. In prolonged cases with internal *hydrocephalus* or block, the site of obstruction may be evident in the region of the roof of the fourth ventricle, the aqueduct, the foramina of Monroe, or in the spinal subarachnoid space. The brain is compressed and flattened and the ventricles distended. In some acute cases the brain stem may be forcibly wedged in the *foramen magnum.*

Insufficient attention has been paid to the *encephalitis* accompanying the infection. Perivascular foci made up of round-cells, pus-cells, red blood-corpuscles, and meningococci may be found throughout the encephalon. Macroscopical areas of hemorrhagic or purulent character may also be found. Changes in the spinal cord and its coverings similar to those found in the cranium may be seen. Intracranial hemorrhage is not infrequent.

Pericarditis, endocarditis, arthritis, pneumonia, pleurisy, empyema, panophthalmitis, empyema of the accessory nasal sinuses, epididymitis, peritonitis, and adrenal hemorrhage may all occur and indicate the widespread invasion of the host by the *Meningococci.* Petechial hemorrhages may be seen on all serous surfaces.

Symptoms.—The infection may be divided into three stages: the first, a local infection of the upper air passages; the second, a general invasion of the blood-stream, or stage of *Meningococcus* sepsis; the third, a stage of metastatic localization usually in the meninges, not infrequently in joints, pericardium, endocardium, lungs, skin, and other regions. These three stages may merge and coexist.

The *first,* or *carrier, stage* may exhibit no symptoms other than the local presence of *Meningococci;* or there may be tonsillitis, pharyngitis, sinusitis, or conjunctivitis with moderate purulent discharge containing the characteristic diplococci.

The *second stage* is one during which the organisms are dispersed by the blood-stream from the initial focus in the upper air passages. Under appropriate conditions, as in military organizations or closely observed epidemics, this stage can be readily recognized by the following features: The patient is dull, apathetic, indifferent; he plaintively resents disturbance, responds in monosyllables with the expenditure of a minimum amount of energy, and prefers to lie on the side with knees drawn up and head bent forward. There is no modulation of voice or play of expression. Silence and immobility are striven for and active delirium or coma are infrequent. This striking deviation from the normal mentality at once arrests the attention of the experienced observer. The oral secretions are dry and viscid, and moderate cyanosis or ashen pallor are common. In 300 cases the initial temperature averaged 101° F. Slight chills are frequent. The pulse is rapid. There is complaint of being "sore all over," and arthralgia or a mild polyarthritis often occurs. The deep reflexes are exaggerated and may be unequal. There is hyperesthesia.

The most distinctive feature is the *rash*, which consists typically of a capillary hemorrhage into the skin and mucous membranes. In size the spots vary from a pin-point to irregular areas 0.5 inch in diameter. They are dusky red, do not vanish on pressure, and fade within three or four days, leaving a rusty stain. *Purpura* is a feature of the fulminating cases. Milder prolonged types exhibit a maculopapular rash resembling the roseola of enteric fever except that the individual spots are larger. Bleb formation, often followed by local gangrene, has been described. *Gangrene* of the toes or of an entire extremity is rarely seen. The leukocyte count is constantly increased, numbering from 15,000 to 60,000, with an average polymorphonuclear percentage of 90.

In this stage meningeal symptoms and signs are absent. The *spinal fluid* is clear and has a normal cell count; it may or may not contain an increased quantity of globulin and an occasional extracellular diplococcus. The nasopharynx and the blood-stream may reveal *Meningococci* provided appropriate methods of cultivation are used. This stage of sepsis may last a few hours or many days or weeks. Rarely the third, or metastatic, stage does not occur at all.

The *third*, or *metastatic, stage* is ushered in by a bursting headache, vomiting, chilly feelings, and fever; frequently, in children, with delirium and convulsions. The patients exhibit retraction of the head, stiffness of the neck, positive Kernig's and Brudzinski's signs; a relatively slow pulse, often with vagus irregularities and the *tache cérébrale*. As the course of the temperature is erratic, no typical chart can be drawn. There may be quotidian or tertian rises, with intervening remissions or intermissions. Afebrile periods lasting for hours or days may be followed by renewals of fever, often with chills. Prolongation of fever beyond the seventh day suggests that treatment is inefficient, that some complication has arisen, or that serum sickness has developed. With increased intracranial pressure the veins of the forehead may become distended and the respiration of the Cheyne-Stokes', Biot, or undulatory type. Insomnia, delirium, and coma may occur.

In the early stages the pupils are dilated; later irregularities appear; and a varying *strabismus* from irritation or paralysis of the oculomotor nerves is frequent. Other rarer findings are fulness of the retinal veins, retinal edema, hemorrhages, or, with internal hydrocephalus, papilledema. Blindness of central origin may occur, but is rarely permanent. Herpes of the lips or face is one of the commonest signs. It is rarely seen before the fifth day and seldom leaves scars. In infants bulging of the fontanels is an important sign. The leukocytosis of the early stages continues. Meningococci have been demonstrated in the leukocytes of the ordinary stained blood-film. Positive blood-cultures can be obtained in from 5 to 80 per cent. of cases; but are most often found in the premeningitic stage when special technic is employed. Except for the initial vomiting the gastro-intestinal tract is not involved. An epididymitis of benign course and outcome may occur in some epidemics. Retention of urine may be overlooked. Bronchitis and broncho- or lobar pneumonia may occur at the onset or as a complication.

In the *fulminating type* there is an overwhelming general toxemia with predominant hemorrhagic skin lesions. The temperature may be subnormal or unusually elevated. Death may occur a few hours after onset. Petechial spots of all sizes and diffuse purpura are typical. Differentiation

from the hemorrhagic types of the exanthemata may be possible only on epidemiological or bacteriological grounds. Meningitis may not occur. The blood-culture is practically always positive.

Atypical meningococcic infections are not uncommon. These may be manifested by prolonged, irregular fever, with arthritic symptoms, petechial or maculopapular rashes, enlargement of the spleen, a positive blood-culture, and extrameningeal foci of infection. Meningitis may not occur or may appear after many weeks of general symptoms.

In no acute disease is the course more variable. Recrudescences and relapses are present in 20 to 30 per cent. of cases. In rare instances there have been several attacks within two years. Among the *complications* are purulent conjunctivitis, panophthalmitis, transitory amaurosis, rarely optic neuritis and retinitis. Otitis media is common. Deafness following involvement of the eighth nerve is usually permanent. Pericarditis and vegetative endocarditis occur. The blood-pressure is low in the stage of sepsis, but with increased intracranial pressure in the later meningitis or block it becomes elevated. An acute arthralgia or polyarthritis is often an initial symptom, and an erroneous diagnosis of *purpura rheumatica* may be made. As a late complication a purulent mono-arthritis, usually of the knee, may occur. The prognosis in such cases is usually good. A third type of arthritis is the effect of serum therapy and may occur seven or more days after beginning the treatment.

Internal Hydrocephalus or Subarachnoid Block.—Most common in infants, this most serious complication arises from organization of exudate in the system of channels through which the cerebrospinal fluid circulates. The subarachnoid block may occur at the roof of the fourth ventricle at the sites of the foramina of Luschka and Magendie, in the aqueduct of Sylvius, the foramina of Monroe, or even in the spinal subarachnoid space. The symptoms may be acute, with unbearable headache, cyanosis of the face, and fulness of the veins of the forehead and retina, delirium, and, not infrequently, sudden death—at times following lumbar puncture; or chronic, with weeks of rapid emaciation, clouded mentality, enhanced meningeal irritability, ocular palsies, and eventual death. Unless relieved by drainage hydrocephalic meningitis is always fatal.

In the early stage of infection, when there are symptoms of a generalized disease, the *cerebrospinal fluid* may be altogether normal and may remain so for hours, days, or, in rare cases, weeks or throughout. As secondary meningitis develops isolated organisms may be found, later globulin, an increase in the number of mononuclear and then of polymorphonuclear cells. When the cell count is more than 400 per cubic millimeter the fluid becomes cloudy; later it may be made very thick with pus-cells, fibrin, and meningococci. The latter are found largely within the pus-cells and are comparatively infrequent in most cases. In general, the presence of a large number of organisms suggests some other form of meningitis. Occasionally the spinal fluid is very thick and coagulates on standing. Blood may be present as the result of the needle puncture or of rupture of the ependymal veins. Dry taps may result from block, from clogging of the needle by too thick exudate, from faulty technic, or without apparent cause. As the infection subsides the cerebrospinal fluid becomes clear, contains less protein, fewer cells, a large proportion of lymphocytes, and fewer organisms or none at all. In some of the prolonged cases the fluid may

become clear, but is under increased pressure, contains slightly increased number of cells, and usually no organisms—the picture suggesting a hypersecretion. Shortly after the onset of meningitis *Meningococci* can be recovered from the cerebrospinal fluid by culture with little difficulty. After serum treatment is under way it is very difficult to obtain a positive culture. A safe clinical rule is to proceed at once with antimeningococcic serum therapy whenever a febrile condition is accompanied by a cloudy cerebrospinal fluid even when organisms cannot be found.

Diagnosis.—Although sporadic cases are common, the presence of an epidemic is an important factor. Meningitis may exist concurrently with other infections. The premeningitic stage may be recognized by the slight fever, the peculiar manner, attitude and facies, the cutaneous vasomotor disturbance or the typical rashes, the marked leukocytosis with polymorphonuclear increase, the heightened and ill-balanced activity of the reflexes, the presence of infection in the upper respiratory tract, the general aching and soreness or arthralgia, and by the demonstration of meningococci in the nasopharynx, by blood-culture, or in the thoroughly centrifuged cerebrospinal fluid. With the onset of definite meningeal symptoms diagnosis is rarely difficult, and the evidence obtained by lumbar puncture is almost always decisive.

Meningismus.—In the *acute infections*, particularly in childhood, symptoms of meningeal irritation may be very prominent and confusing. Scarlet fever, influenza, typhus fever, pneumonia, mumps, gastro-enteritis, and tonsillitis may be attended by headache, vomiting, stiffness of the neck, and positive Kernig's signs. During these diseases, however, the cerebrospinal fluid is clear and rarely contains an increased number of leukocytes. Fifty or more cells per cubic millimeter may be present, but the fluid does not become purulent and the development of the original disease makes the picture clear. In the differentiation of influenza and typhoid fever from meningococcic infection the lack of leukocytic increase in the blood in both these diseases is decisive. While the maculopapular eruption so common in typhoid fever is occasionally seen in meningococcic infections, the longer incubation period, the longer, more regular duration with abdominal symptoms, the more uniform picture, and the positive bacteriological or serological evidence of typhoid provide means of differentiation.

Sepsis with meningeal or cerebral metastasis may give a confusing picture. The port of entry, the frequent involvement of the endocardium, the bacteriological evidence obtained from blood-culture and from direct examination of the spinal fluid, usually serve for differentiation. The petechiæ accompanying the common types of streptococcic sepsis are much smaller than the hemorrhagic spots seen in meningococcus infection. The cerebral form of poliomyelitis, in contrast with meningococcic meningitis, often begins with symptoms of a gastro-enteritis. The temperature is higher at the onset and declines more promptly, while herpes and hemorrhagic eruptions are absent and the evidence of meningeal irritation is usually less. The spinal fluid shows a higher proportion of lymphocytes and the bacteriological evidence is, by ordinary methods, negative. The reflexes are usually diminished and paralysis common. *Tetanus* may be differentiated by the paroxysmal character of the attacks—the trismus, the history of a wound, the absence of headache, and the lack of pus-cells in the

cerebrospinal fluid. In *tuberculous meningitis* the history of similar infection in the family, the slower onset, the evidence of tuberculosis elsewhere in the body, the absence of hemorrhagic rashes and of marked leukocytosis, rarely the finding of choroidal tubercles, the lesser increase in the number of cells in the spinal fluid, and the presence of tubercle bacilli usually serve to clear up the problem.

Septic meningitis caused by the common pyogenic organisms is usually secondary to a focus in the middle ear, the accessory nasal sinuses, scalp, or face. Organisms are usually abundant in the cerebrospinal fluid, which becomes rapidly thickened by pus; and the course is usually very short and fatal. Other conditions which are rarely confused with meningococcus meningitis are *delirium tremens, rheumatic fever* with cerebral involvement, *diabetic coma, uremia, tetany,* and *cerebral abscess, hemorrhage,* or *thrombosis.*

Prognosis is extremely difficult, and one can never safely predict what is going to happen in a given case of meningococcic infection. The general mortality rate is still high, averaging above 50 per cent. for the country at large. If the disease is recognized and serum treatment begun within forty-eight hours of onset the mortality should not be more than 15 per cent. If treatment is deferred beyond the second day the mortality rises above 20 per cent. The rate increases directly according to the time which has elapsed between the onset of the disease and its treatment. In patients less than three years of age meningococcus meningitis is very fatal. Of most favorable import is prompt response to serum treatment. Failure to respond promptly to serum treatment is ominous. The outlook is better in cases with gradual onset than in those in which the complete picture develops within a few hours. An extensive petechial eruption attends grave cases. Patients with diffuse purpura practically always die; those with hydrocephalic complications, pneumonia, or endocarditis seldom recover. An early polyarthritis or a marked ocular palsy are serious. With general recovery involvement of the cranial nerves usually clears up except when the eighth nerve is attacked. Deafness from this source is usually permanent. The mortality in the early phases of an epidemic is generally higher than toward the end.

Treatment.—The First, or Carrier, Stage.—The precise value of antiseptics or vaccines used to eradicate meningococci from the upper air passages is not known. It must be recognized that in two-thirds of the cases these organisms disappear spontaneously. In general, it seems better to trust to nature than to impair the integrity of the mucous membrane by strong antiseptics. If there is obvious disease of the tonsils, paranasal sinuses, or pharynx, this may be eradicated by surgical means; and such measures are often followed by disappearance of meningococci. The local use of antiserum in the throat or the subcutaneous administration of vaccines may be tried. Fresh air, sunlight, and time are our chief reliance in dealing with the carrier.

The Stage of Sepsis.—The chief resource during the stage of sepsis is the intravenous use of *antimeningococcic serum.* This should be given with the utmost dispatch, as an hour's delay may be sufficient to turn the balance adversely. As in treatment of diphtheria or tetanus, adequate amounts of the antibody must be used—better an excess than too little. In adults an average dose of 100 c.c. of serum should be given every twelve hours in the average case; every eight or even every six hours in the gravely infected

for three or more doses or until the desired result is obtained. The usual precautions in giving serum should be observed. A preliminary injection of *morphin* and *atropin* is desirable. Sensitiveness is determined by intradermal test. If possible, a preliminary subcutaneous injection of 0.5 c.c. of serum should be given and the larger amount injected only if no symptoms occur. The full dose should be given with the utmost care, the first 15 c.c. being injected at the rate of 1 c.c. per minute. If nausea, pallor, sweating, collapse, urticaria, dyspnea, or similar alarming symptoms occur, the flow must be stopped. It may be renewed with caution after a few moments. If no trouble arises during injection of the first part of the dose, the remaining amounts may be allowed to run in more rapidly. Once the first dose has been given, subsequent injections can be made with less danger of immediate serum reactions. By such massive intravenous therapy it is sometimes possible to abort the disease—at any rate to mitigate its later phases.

The Metastatic Stage.—Under ordinary clinical conditions meningitis is rarely recognized before the metastatic stage, when the meninges are fully involved. Experience has shown that even in this stage the intravenous administration of serum by the method just described is beneficial, and should be carried out in every case. In addition, the intraspinal injection of serum should be made in the average case once in twenty-four hours. By lumbar puncture sufficient fluid is withdrawn to reduce the pressure to normal, namely, until the flow is about 1 drop per second. Usually from 20 to 50 c.c. of purulent fluid are withdrawn. From 20 to 35 c.c. of serum are then allowed to run in by gravity, never injected forcibly. It is well to give about 5 or 10 c.c. less of serum than the amount of cerebrospinal fluid withdrawn. Respiratory embarrassment must be carefully watched for during this maneuver. If it occurs, a small amount of fluid can be withdrawn until the symptoms stop; the treatment can then be renewed. Intraspinal treatment should be continued daily until control of the symptoms is shown by a decline in temperature, decreasing turbidity of the spinal fluid, the absence of organisms, and the return of mononuclear cells. It is well to continue to drain the subarachnoid space by lumbar puncture daily or on alternate days even after this stage. Such drainage gives a hint as to the not infrequent return of the infection, and provides data for the renewal of vigorous treatment by vein and spine. Drainage also tends to prevent the development of block. It is possible to overdo treatment in the later phases of the disease. If intraspinal treatment is followed by evidence of increased meningeal irritation it is sometimes well to omit all interference or to continue drainage alone; or complete inaction at this stage may be followed by prompt clearing up of the entire picture. If prompt benefit does not follow the intensive serum treatment something is wrong. The patient may have an overwhelming infection which will cause death speedily, or the type of serum used may not contain antibodies specific for the type of meningococcus concerned. The physician must remember that serum effective against the regular type of meningococcus may not be efficacious in treating cases infected with the parameningococcus or some of the intermediary types. If possible the serum employed should be tested for its agglutinin content against the meningococcus isolated from the patient's nasopharynx, blood-stream, or cerebrospinal fluid. Ordinarily, to be effective, this serum should agglutinate in a

dilution of at least 1 : 200. If it does not agglutinate in a dilution of 1 : 50, it is rarely beneficial. If such a test is not feasible, serum from another source should be promptly used, since another serum may contain the antibody lacking in the serum originally used. Such change in serum is often the means of saving life.

Cause of Continued Symptoms.—Seven days after the beginning of serum treatment *serum sickness* may cause moderate or even high temperature, erythema, urticaria, swelling of the lymph-glands, enlargement of the spleen, or arthritis. *Panophthalmitis* may be accompanied by an elevation of temperature; so also may *otitis media, pericarditis, endocarditis, meningococcic arthritis, hydrocephalus,* or other late complications. Occasionally *abscess of the cerebrum* may pursue a prolonged febrile and fatal course. Serum sickness demands no special treatment. Subcutaneous injections of 5 to 10 minims of adrenalin may give transitory relief. An eye destroyed by purulent invasion should be enucleated after several weeks have elapsed in order to give a chance for thorough walling off of the focus. Pericarditis with effusion should be treated by aspiration and local serum injection. Endocarditis is usually evidenced by positive blood-culture and is likely to be fatal, but active intravenous treatment should be persistently tried. Arthritis should be treated by rest and, if much effusion is present, by aspiration and the injection of serum. Hydrocephalic meningitis or block demands energetic and prompt measures. Drainage must be effected within a few days if death is to be prevented. Drainage can often be secured by puncture of the *cisterna magna.* This should always be resorted to if lumbar puncture does not give a free flow of fluid. Serum can be administered by this route. Puncture of the lateral ventricles is a simple procedure in children, and should be carried out without hesitation when there is evidence of obstruction in the subarachnoid space. Serum can be easily given by this method. In adults, if drainage by the lumbar or cistern route is unsuccessful, ventricular drainage can be accomplished by trephining the skull. Sometimes a combination of lumbar and cistern puncture, or of cistern and ventricular puncture with through-and-through irrigation with salt solution or serum, is effective in securing drainage. In the acute swelling of the encephalon in the early stages of the disease, which is often shown by bursting headache, cyanosis, full veins of the forehead, and marked delirium, the attempt to reduce the volume of the cranial contents by the administration of hypertonic salt solution intravenously or by the giving of sulphate of magnesium by mouth is advisable. Venesection may also be of use in selected cases. Involvement of all the cranial nerves except the eighth usually clears up spontaneously with time. Deafness caused by involvement of the eighth nerve in this disease is usually permanent. It is possible that relapses may be guarded against by the use of vaccines during convalescence. The administration of three or four doses of 500,000,000 killed meningococci at weekly intervals may be advised.

W. W. Herrick.

GONOCOCCUS INFECTION

Definition.—Infection with the *gonococcus* results in a *primary focus*, usually in the genital tract, which may or may not lead to the formation of *secondary foci*. While the *primary focus* is usually in the genito-urinary tract, it is not infrequently in the conjunctiva in newborn infants (*ophthalmia neonatorum*) and may rarely occur in the mouth or rectum. *Secondary foci* may result from direct extension of the infection to structures in the neighborhood of the primary focus, particularly if these communicate with the site of the primary focus by ducts or similar channels. Secondary foci may also occur at a distance from the primary focus by *metastasis*, the infecting organisms gaining access to the general circulation through the blood- or lymph-vessels.

History.—Gonorrhea is certainly as old as recorded history and presumably much older. References to the disease are found in Leviticus, in the oldest Egyptian papyri, and in the ancient writings of the East Indians and Chinese. The word itself means "flow of semen," and this idea of the nature of the disease, which was originated probably by the Greeks, dominated the medical and lay mind for centuries. According to Gluck, Sebastianus Petritius (1591) was the first to state that the discharge was pus and that the lesion was in the penis.

The contagiousness of the disease was not appreciated until the Middle Ages, when Lanfranchi and others began to point out that contact with infected persons was necessary for transmission. Gonorrhea was not differentiated from the other venereal diseases until early in the nineteenth century, when the extensive experimental work of Philip Ricord on its inoculability definitely cleared the matter up. A great step forward was made in 1879 when Albert Neisser discovered the causal agent. Exact knowledge of the relationship of gonorrhea to its complications, near and remote, has been obtainable only since that time.

Incidence.—No accurate figures covering the incidence of gonorrhea among the general population are available. Physicians are unwilling to report cases by name, and many patients never consult a physician, but are treated by advertising quacks and druggists. The recent figures of Jaeger show that in Switzerland approximately 20 persons per 10,000 of the population contract venereal disease each year, and of these, about 75 per cent. have gonorrhea. Among the new cases, males preponderate over females in the proportion of 3 to 1. The rate among divorcees is 130 per 10,000; among the single, 70 per 10,000; among the married, 38 per 10,000; and in widowers, 17 per 10,000. These figures are given so that the reader may form some idea of the prevalence of gonorrhea in a civilized nation. Doubtless accurate figures would show considerable differences in different localities. According to Casper, 20 per cent. of gonorrheics have complications. These are most commonly local. Jagic and Schaffner state that general gonorrheal septicemia occurs in only 0.7 per cent. of treated cases. In all cases of arthritis, however, and in other metastatic complications there must be a temporary invasion of the blood-stream, so that the above figures do not represent the proportion of cases in which the blood is invaded.

Etiology.—The usual source of gonorrhea is exposure to an infected individual during sexual contact. In newborn infants infection of the eyes may occur during the passage of the child through an infected birth canal. In the vulvovaginitis of infants and young children the disease is not venereal in origin. In many such cases the source of contagion is not demonstrable, but in institutions, such as hospitals and asylums, widespread outbreaks may follow the admission of an infected child because of

transmission of the infection by thermometers, sponges, bath water, bed linen, etc. Gonorrhea of the mouth and rectum is transmitted through improper practices.

There are apparently few predisposing factors of importance. Infected coitus while under the influence of alcohol is thought by some to predispose. Excessive coitus may undoubtedly light up latent infections, and in this way newly married women may become infected by husbands who before marriage believed themselves cured of the disease.

Bacteriology.—The organism causing gonorrheal infection is the coccus described by Neisser in 1879. The organisms occur in pairs, the individual members being kidney shaped or biscuit shaped, with their concave surfaces facing each other. They are usually found within leukocytes, and do *not* stain by Gram's method. Cultivation is difficult and was first accomplished by Bumm in 1885. On ordinary media there is usually no growth, but on special media, such as blood-agar, testicular-agar, chocolate-blood-testicular-agar or yeast-testicular-agar, growth may be abundant. Moisture is very necessary to growth, but the amount of oxygen should be limited. Torrey was the first to emphasize the fact that there are different strains of gonococci; as many as twenty-seven have since been described. According to Jotten, there are marked differences of virulence in different strains, and patients with severe and complicated attacks are infected with the more virulent types. There is little opportunity to confuse the *gonococcus* with other organisms in the genito-urinary tract, but in eye infections the *meningococcus* and the *Micrococcus catarrhalis* must be differentiated. Occasionally, the ordinary pus staphylococci strongly resemble the gonococcus in smears. All these organisms, however, are easily cultivated on ordinary media and stain by Gram's method.

Symptoms.—The local complications of gonorrhea—such as epididymitis, vesiculitis, prostatitis, pyelitis, bartholinitis, and pyosalpinx—are usually regarded as surgical, while the eye complications naturally fall to the ophthalmologist. The metastatic complications, iritis excepted, are assumed to come within the scope of internal medicine and are those here considered.

Metastatic complications seldom occur in the male unless the posterior urethra is involved, and in both sexes they are favored by certain accessory factors. Continuation of strenuous work during an attack of gonorrhea favors *arthritis*, and excesses of an alcoholic or sexual nature, careless instrumentation, and debilitating general diseases, such as diabetes, may also play a rôle. In the female, *pregnancy* and *menstruation* are important predisposing factors. Jotten's work indicates that the *virulence* of the infecting strain of organism is more important than was formerly supposed to be the case.

Gonorrheal Septicemia and Endocarditis.—*Gonorrheal septicemia* occurs but seldom—according to Jagic and Schaffner in only 0.7 per cent. of all treated patients. It is not infrequently associated with other evidences of metastasis, such as arthritis; and it may or may not be accompanied by endocarditis. Thayer's figures indicate that a trifle over 11 per cent. of the cases of *acute endocarditis* are due to the gonococcus. This is a much higher percentage than is given by most authors. Septicemia with or without endocarditis may occur at any period of a gonorrheal infection, even when all signs of local activity have disappeared.

The symptoms presented are those of general sepsis and, when endocarditis is present, of embolism also. The *onset* of the illness is usually acute. The patient has high fever, often accompanied by chills. Leukocytosis is present and anemia may be a prominent feature. The common *embolic manifestations* are petechiæ and pulmonary, splenic, or renal infarction. Cerebral emboli are not uncommon. The aortic valve is the one most frequently attacked, but the valves of the right side, especially the pulmonic, are more frequently involved than in most forms of acute endocarditis. The acute endocarditis may involve an already damaged valve. *Myocarditis* and *pericarditis* may occur. The duration of the process, when endocarditis is present, averages between two and three months. Recovery from gonorrheal septicemia occurs occasionally, and there are cases on record of patients with obvious cardiac complications who got well, but these are exceptional. As a rule, the outlook is definitely bad.

Gonorrheal Arthritis.—This is by far the most common and, therefore, the most important of the metastatic complications. Leaving aside the not infrequent instances of *arthralgia*, the following types may be recognized:

1. *Acute Gonorrheal Arthritis;*
   (*a*) Serofibrinous.
   (*b*) Phlegmonous.
2. *Chronic Gonorrheal Arthritis;*
   (*a*) Hydrops.
   (*b*) Ankylosing form.

The commonest type of gonorrheal arthritis is the acute *serofibrinous form*. It usually occurs as a polyarthritis affecting most commonly the joints of the knee, foot, and hand. *Fever* is present at the onset and the affected joints are very painful, swollen, and often fluctuant, with reddening of the overlying skin. This may continue for several weeks and may be followed by resolution, by a chronic arthritis with hydrops, or, more rarely, by suppuration.

The *phlegmonous form* is decidedly rare and is sometimes due to mixed infection, though the gonococcus alone is capable of causing it. The patient usually has *high fever* and *severe constitutional symptoms* from the onset. The affected joints are intensely painful, but effusion is less marked than in the ordinary form, and involvement of the periarticular structures with marked tissue destruction is a prominent feature.

Chronic hydrops of gonorrheal origin is often insidious and painless in onset, but may follow an acute arthritis. Large joints, particularly the knees, are apt to be involved. The process is usually monarticular and constitutional symptoms are often lacking. The patient may discover the swelling by accident, although limitation of motion may call attention to it. Where large effusions are present there may be excessive mobility. In some instances the process ceases spontaneously; in others it is stubborn and resists all forms of treatment.

The *ankylosing form*, which resembles infectious deforming arthritis due to other organisms, is very uncommon.

Other portions of the *locomotor system* which may be affected by metastatic gonorrhea are the bursæ, tendon sheaths, muscles, periosteum, and

bone. Most commonly these tissues are involved in connection with gonorrheal arthritis, the bursæ, tendon sheaths, or muscles in the immediate neighborhood of an inflamed joint being invaded by direct extension of the lesion. Occasionally gonorrheal bursitis, tenovaginitis, myositis, or osteoperiostitis occur as isolated phenomena. The occurrence of most of these lesions, except as complications of arthritis, is so uncommon that they cannot be discussed in detail in a work of this scope.

There is one lesion, however, which deserves fuller notice. This is the *painful foot* of gonorrhea. This is of two types:

(1) Inflammation of the bursa between the Achilles tendon and the *os calcis*, and (2) inflammatory exostosis on the inferior surface of the *os calcis*. The former gives rise to so-called *achillodynia*, the latter to the "painful heel" of gonorrhea.

Metastatic involvement of the *blood-vessels* in gonorrhea is rare, and is usually an accompaniment of other lesions. A local thrombophlebitis of the veins of the penis is occasionally noted. Thrombophlebitis of peripheral veins most commonly attacks the internal saphenous vein of the right leg. As in thrombophlebitis due to other organisms, the symptoms are local pain, tenderness over the vessel involved, and local edema. The thrombosed vein may often be felt as a tender cord.

Pulmonary complications of gonorrhea are decidedly uncommon. When gonorrheal endocarditis is present there may be pulmonary embolism with infarct. This may lead to a secondary pleurisy. In rare instances primary pleurisy may occur. Embolic pneumonia is a rare complication and may be accompanied by expectoration of gonococci.

Skin Manifestations.—The skin manifestations of gonorrhea are practically always an evidence of generalization of the virus. The most characteristic type of gonorrheal skin disease is *hyperkeratosis*. This usually involves the palms and soles, and takes the form of light red, slightly elevated, sharply circumscribed areas varying from a few millimeters to 1 or 2 cm. in diameter. The lesions are often somewhat indurated, with a scaly surface over which the hyperkeratotic areas are distributed. The resemblance to *psoriasis* is often striking. Occasionally erythematous or papular eruptions occur, and hemorrhagic eruptions have also been noted.

Nervous Manifestations.—The exact relation of gonorrhea to *nervous manifestations* is still a matter of discussion. It is generally assumed that involvement of the nervous system is toxic rather than metastatic, although such lesions as gonorrheal meningitis are undoubtedly due to metastasis. *Neuralgias* in the nerve territory involved in local gonorrheal lesions are the commonest lesions. *Sciatica*, especially in the male, may accompany the late stages of gonorrhea, particularly when the prostate and seminal vesicles are infected. Neuralgias of the pudendal nerves, the tibial nerve, or the nerves supplying the Achilles tendon may also occur. True *neuritis*, which may be accompanied by extreme muscular atrophy, has been occasionally noted. *Myelitis* is a rare complication.

Gonorrhea may also play a rôle in the production of *neuroses* and *psychoses*. Sexual neurasthenia and nervous impotence in the male are frequently associated with chronic gonorrhea. In the female the disease may be indirectly responsible for various neuroses and psychoses associated with sterility.

Diagnosis.—The diagnosis of a metastatic complication of gonorrhea depends on four factors:

1. The history of a recent attack of gonorrhea or the discovery of a primary or a local secondary focus.

2. The demonstration of Gram-negative, intracellular diplococci in the inflammatory exudate from a local or metastatic focus.

3. The cultivation of the gonococcus from inflammatory exudates or, in the case of general septicemia, from the blood.

4. A positive gonococcus complement-fixation test.

The reproduction of the disease by inoculation of a susceptible individual, while clinching the diagnosis, is seldom permissible as a practical procedure.

In septicemia a negative blood-culture is not without importance inasmuch as the common causal agents of acute endocarditis are so readily cultivatable.

In all cases of suspected metastatic gonorrhea evidences of a local focus of gonorrhea must be carefully sought for. Not only must the urethra be carefully examined, especially early in the morning before urination, but the prostate and seminal vesicles in the male, and the vagina, cervix, adnexa, and Bartholin's glands in the female, must be examined, and smears of such exudate as may be obtainable must be searched for the characteristic organisms. If feasible, cultures should be made on special media. The *complement-fixation test* has been somewhat discredited in the past, but there is a decided tendency to rehabilitate it. The work of Barringer and Williams and others shows that, particularly in the case of gonorrheal complications in women, the test may be of great value.

Prognosis.—The prognosis of a metastatic complication of gonorrhea depends on its nature. In general gonorrheal sepsis without endocarditis the prognosis, while exceedingly grave, is not necessarily fatal. Where sepsis is complicated by endocarditis recovery, while not unknown, is hardly to be expected.

The outcome of local metastatic complications, with the exception of those involving the central nervous system, is generally favorable, though here again the localization and type of lesion is important. The ordinary serofibrinous gonorrheal arthritis usually results in recovery with retention of good function, though varying degrees of disability in single joints are not unusual. In the phlegmonous and ankylosing types of arthritis crippling is the rule. In involvement of bursæ, tendons, and bones the outlook is usually good unless extensive destruction of tissue occurs. This rarely happens.

In the case of the pulmonary and skin lesions, which practically always accompany general sepsis, prognosis depends on the general rather than the local condition. The outcome of the nervous and mental complications is usually good with appropriate treatment, including the elimination of the primary focus of disease.

Treatment.—In all forms of metastatic gonorrheal infection the first essential in treatment is *the eradication of the primary focus of disease.* This may be accomplished by the usual local treatment, but it may involve the surgical removal of diseased tissues, as in gonorrheal salpingitis for example.

During the acute stages of *non-destructive local inflammatory processes,*

such as the ordinary arthritis, the general principles of local and general rest, the application of heat or cold, the relief of severe pain, nourishing food, the free administration of fluids, care of the bowels, and provision for sleep govern treatment. As the local processes, particularly the joint affections, become more chronic, massage, passive motion, and other forms of physiotherapy are to be employed.

Destructive lesions, such as the phlegmonous type of arthritis, call for prompt and often radical surgical intervention, with removal of necrotic tissue, free drainage, and the use of antiseptics.

In *gonorrheal sepsis* general supportive and eliminative treatment is indicated. The patient should be in bed, preferably in the fresh air. The diet should be soft and nourishing, and free consumption of fluids should be encouraged. The bowels should be kept open by a daily saline enema. At times laxatives may be necessary. Sufficient sleep should be provided for, if necessary, by the aid of sedatives. High fever should be combated by hydrotherapy. In severe anemia transfusion may be employed. Cardiac stimulation should be administered if indicated.

The use of *sera* and *vaccines* in the treatment of local gonococcal metastases is still subject to discussion. So far as *antigonococcus serum* is concerned the results have been so conflicting that this form of treatment has been almost abandoned. There is reason to believe, however, that *vaccine* treatment has a definite place, especially in the subacute and chronic stages of local gonorrheal processes. The vaccines now in use are generally polyvalent and are made from several strains of gonococci, as Teague and Torrey first suggested. The dosage depends on the patient's reaction and varies from 5,000,000 to 500,000,000 micro-organisms. Most authors recommend beginning with a small dose and gradually increasing. The vaccines may be given as often as every other day, but are most commonly injected at five-day intervals. In an average case an initial dose of 5,000,000 bacteria with an increment of 5,000,000 every five days is likely to be satisfactory. If the reaction to the first dose is pronounced, a longer interval and a more gradual increase in dosage is desirable. If the reaction is slight, the interval may be shorter and the dosage may be increased more rapidly.

A form of treatment which has come into vogue in recent years is "*protein shock therapy*." This is based on the principle that the introduction of an alien protein into the system causes a non-specific reaction which stimulates the body processes concerned in the production of immunity. The technic of the treatment consists in the intramuscular or intravenous injection of pure albumose, or of sterilized milk or bacteria (typhoid vaccine) into the patient. If typhoid vaccine is used, from 5,000,000 to 250,000,000 bacteria administered intravenously in normal saline solution may constitute each dose. It is wise to begin with small doses in order to determine the severity of the reaction. If sterilized milk is used, the patient will become more or less sensitized ten days after the injection. Further injections must, therefore, be given with great caution and at short intervals (three to five days). The foreign protein reaction is very unpleasant and is characterized usually by a severe chill, headache, and general aching lasting half an hour or longer. The reaction is accompanied by a leukocytosis and a rise in blood-pressure, so that this form of treatment must be used with caution in hypertensives. In patients with a history of allergic diseases the treatment must also be used with great caution. A few deaths

have been reported when the condition of the patient before injection was poor. There is no doubt that in some patients with gonorrheal arthritis the reactions lead to improvement in the joints. Some patients refuse to continue the treatment for more than a few doses on account of the severe reactions.

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TYPHOID FEVER

Definition.—Typhoid fever is an acute general infection with the *Bacillus typhosus*, which is characterized especially by involvement of the lymphoid tissues, usually with marked hyperplasia and ulceration of Peyer's patches, and with enlargement of the spleen. Clinically, the disease is characterized by a continued fever, leukopenia, relatively slow pulse, and a rose-colored eruption, occurring usually in crops.

History.—The first highly suggestive description of typhoid fever was made by Willis in 1643. He observed an epidemic among soldiers and also a house epidemic in which 5 members of a single family were attacked one after another within a period of four months. He described in one patient symptoms suggestive of a perforation of the intestines. Early in the nineteenth century French physicians, by pathological studies, were able to differentiate the disease as an entity; and Louis in 1829 suggested the name "*Fièvre typhoide.*" Even he, however, no doubt confused typhoid and typhus fever. Gerhardt, of Philadelphia, a student of Louis, on his return to America was fortunate enough to observe an epidemic of both typhoid and typhus, and in 1837 published the article which first clearly differentiated these two diseases. Murchison was one of the first to suggest that the infection was contained in the feces, and Budd, in England in 1856–60, published a series of papers in which he emphasized the importance of the feces as a means of disseminating the disease. Eberth in 1880 discovered the typhoid bacillus and was able to show its probable etiological relation to the disease.

Incidence.—Typhoid fever is preventable, and its incidence is an indication of the efficiency of health agencies. No country is free from the disease. The death rate from typhoid for the year 1909 10 in ten large European cities was 2.86 per 100,000 population. During this same period in ten large American cities the mortality was 23.1 per 100,000 population. In 1923 this figure had been reduced to 2.6 per 100,000, and in 57 American cities with a total population of 27,365,000 the death rate was 3.45 per 100,000. The smaller cities and rural districts have, on an average, a higher incidence of typhoid.

Armies, both in peace and war, suffer severely from the disease. The American Army in the Spanish-American War, with a mean strength of 107,973, had 20,708 cases of typhoid, with 1580 deaths. The British Army, with a strength of 380,605 during the Boer War, had 57,684 cases, with

8022 deaths. During the recent World War there was a total of 213 deaths from typhoid in the entire American Army from September 1, 1917 to May 2, 1919. This is the best evidence of the advancement made in prevention.

Season.—Typhoid fever is distinctly a seasonal disease. A curve of the registration area in the United States shows that the minimum number of cases develops in June; there is then a gradual increase, which reaches a maximum in October; then a gradual fall until December, followed by a secondary rise; then a gradual return to the minimum in June.

Sex.—The male sex furnishes slightly more than half the number of adult patients; in childhood the two sexes are equally susceptible to the infection.

Age.—The greatest susceptibility to typhoid is during youth and early adult life. More than 50 per cent. of the individuals attacked are between the ages of fifteen and twenty-five years.

Immunity.—A number of individuals may partake of the same contaminated food or water and only a small proportion contract the disease. Such natural immunity is largely relative, and probably could be overcome by massive infection.

There is a *temporary acquired immunity* after the disease, but this is less permanent than that conferred by some of the acute exanthemata. About 2 per cent. of all typhoid patients have had a previous attack.

Etiology.—Bacteriology.—The *Bacillus typhosus* is a non-spore-forming, actively motile bacillus 1 to 3 micra in length and 0.5 to 0.8 micra in diameter, which is aërobic and grows best at the body temperature. It does not liquefy gelatin, is readily stained, and is Gram-negative. It grows well in a variety of media, especially agar, gelatin, bouillon, milk, blood-serum, and potato. It may be differentiated from the colon bacillus by its greater motility, and its failure to produce gas in dextrose media or acid in lactose media. It does not, therefore, curdle milk. Under ordinary cultural conditions the bacillus does not form indol. Cultures are destroyed in ten minutes by a temperature of 140° F., but the organism may live in ice several months.

Distribution in the Body.—Typhoid bacilli may be present in the blood, feces, or urine; and as a result of distribution by the blood they may be found in the various organs of the body, especially in the spleen, lymphatic glands, bone-marrow, and gall-bladder. The bacilli are present constantly in the blood during the first week of the disease. During this period they are rarely in the stools. Apparently the disease in its incipiency is a generalized infection, the lymphoid tissues, including Peyer's patches, become secondarily infected. Multiplication of the organisms does not take place primarily in the intestines, as is shown by inability to obtain positive stool cultures early in the disease. Autopsy examinations show that the organism is most abundant in the duodenum, and that its numbers decrease toward the lower part of the intestinal tract. This suggests that the typhoid bacilli in the stools are derived largely from the biliary tract. In other words, the bacilli after ingestion reach the blood-stream and are distributed to various parts of the body, multiplying especially in the lymphoid tissues. They are eliminated into the intestine from the biliary tract and ulcerating Peyer's patches.

Channels of Exit of the Typhoid Bacilli.—The chief channel of elimination is through the intestinal and urinary tract. The vomitus when it contains

regurgitated duodenal contents may contain the bacilli. While the organism is not always demonstrable in the feces, it is probably always present. The bacilli are most abundant during the second week, and gradually disappear, as a rule, by the end of the sixth week except in intestinal carriers. Typhoid bacilli are found in the urine in about 25 per cent. of the cases. They disappear during convalescence except in urinary carriers.

Modes of Infection.—The typhoid bacilli, leaving the body through the feces and urine, find their way in some manner to the intestinal tract of a susceptible individual. If it were feasible to destroy all typhoid bacilli as they leave the body typhoid fever would disappear. The multiplication of the organisms outside the body is practically negligible and their period of viability brief.

Water.—This is the chief source of infection. A community with a good water-supply is protected from an extensive epidemic. In the city of Hamburg, which formerly obtained its water-supply from the river Elbe, there were 15,804 cases of typhoid from 1885 to 1888; with the instillation of a suitable water-supply typhoid practically disappeared. The water-supply may be contaminated by sewage, by bathers and campers, or by surface drainage after heavy rains. If the body of water is sufficiently large, steamships may become a source of trouble.

Ice.—When water freezes the majority of typhoid bacilli are promptly destroyed. An epidemic at St. Lawrence State Hospital, Ogdensburg, N. Y., was, however, traced to ice.

Milk.—When milk is infected the organisms are acquired by either contact contamination or washing the utensils or diluting the milk with contaminated water. A typhoid carrier or a typhoid patient may transfer the bacilli by direct contact. A common source of trouble is typhoid in the milk handler's family. An extensive epidemic in Washington, D. C., was traced largely to milk.

Ice-cream.—Circumscribed epidemics have been traced to ice-cream.

Butter and Cheese.—It has been shown that typhoid bacilli can live in butter for three weeks. No epidemic has been traced to this source. Cheese is an unimportant source of infection.

Shell-fish.—*Raw oysters* are frequently responsible for limited epidemics of typhoid. The contamination occurs when the oysters are transfered from the beds to some place near shore—frequently near the mouth of a fresh-water stream—where they are kept for convenience or fattening. If the water is contaminated by sewage or other means, the oysters take up the micro-organisms and may infect anyone who eats them.

Flies.—When flies are permitted to come in contact with the excreta of typhoid patients the bacilli may adhere to their feet or bodies, or be ingested, and later appear in the feces. In this way flies may act as typhoid carriers, and by contaminating food become an important factor in disseminating the disease.

Dust.—When the excreta of typhoid patients are mixed with the soil, which later becomes dry and powdered, the germs may be carried in the dust. It is believed that dust-borne typhoid was quite common in both the Boer and Spanish-American Wars.

Contact.—Infection by contact may include those cases in which the infection takes place by immediate transfer from the infected to the healthy. Previous to the days of protective vaccination those who cared for typhoid

patients frequently contracted the disease. Friends or relatives in intimate contact with the patient incurred the same risk. When deposited on bedding the typhoid bacillus survives only a few days, but sufficiently long to permit contagion. The difficulties of avoiding contact infection are greatly increased by the prevalence of mild or unrecognized typhoid, and especially by the existence of carriers.

Carriers.—Individuals who recover from typhoid may continue to harbor virulent bacilli for months or years. As the blood of nurses who care for typhoid patients quite frequently contains typhoid bacilli in spite of the lack of any other signs or symptoms of the disease, it is to be inferred that a considerable number of cases of typhoid are unrecognized. Apparently about 2 per cent. of typhoid patients become chronic intestinal carriers; a smaller number, urinary carriers. It is claimed that about 80 per cent. of the chronic carriers are women. To the list of carriers, from the standpoint of contagion, should be added the large number of cases of ambulatory typhoid which occur in every epidemic. The actual menace of a carrier depends in a large measure upon his habits of cleanliness and occupation. Carriers who are food handlers are especially dangerous—cooks, for example, and waitresses, marketmen, dairymen, and other milk handlers. "Typhoid Mary," a cook, had been employed in seven families during a period of years, and in each family typhoid fever developed; 28 cases in all were directly traced to her.

Morbid Anatomy.—The most characteristic changes are found in the intestinal tract. Peyer's patches early become hyperplastic and project above the level of the surrounding mucosa. Microscopically, at this stage there is evidence of marked hyperemia with perifollicular hyperplasia. In addition, many large round phagocytic cells are present; these may eventually outnumber the small round cells. By the beginning of the second week portions of the follicles undergo a form of coagulation necrosis. This is due to vascular obstruction which is largely brought about by pressure from the surrounding hyperplastic tissue. The central portion of the plaques sloughs away first, leaving a smooth base. The edges of the ulcer, however, remain swollen and infiltrated for some time. The base of the ulcer may be the muscular coat, but the lesion may extend entirely through the wall and cause perforation. It is during the stage of sloughing that hemorrhages are most apt to occur.

The characteristic typhoid ulcer is somewhat oval, with its long axis parallel to the long axis of the bowel. The base is usually smooth, the edges thin and undermined. The most advanced ulcers are usually found in the ileum in the region of the ileocecal valve; while those which are less well developed appear higher in the tract. In very severe cases the lower end of the ileum may be converted into one large ulcer, only islets of mucosa remaining.

The process of healing depends on the intensity of the lesions. Not all Peyer's patches undergo necrosis. Where the process is less marked the hyperplastic elements are absorbed and the plaques return to normal. Where sloughing has occurred the borders beyond the necrotic area become hyperemic and hemorrhagic, and infiltration may occur, probably accounting for the late hemorrhages. Gradually the cellular elements in the periphery proliferate and extend over the denuded area until the original continuity of the epithelium has been restored. When ulceration has been very extensive, restoration may be incomplete, so that the floor of the Peyer patch

is covered with connective tissue containing few or no glandular elements. Healed ulcers may often be recognized by their smooth pigmented surface, which is frequently depressed below the surrounding mucosa. Typhoid bacilli may be detected in the hyperplastic areas before necrosis sets in.

Perforation is responsible for about 3 per cent. of the deaths from typhoid. In the majority of instances it occurs in the ileum within 18 inches of the ileocecal valve, but it may take place in any portion of the large intestine, including the appendix and rectum. It is rare in the jejunum. General peritonitis follows perforation, and may in rare instances develop without actual perforation.

Mesenteric Glands.—Hyperemia and hyperplasia of the mesenteric glands develop synchronously with the involvement of Peyer's patches. These glands may reach the size of a walnut and often contain necrotic areas. In other cases they may suppurate, rupture, and give rise to peritonitis. As a rule, the glands about the lower end of the ileum are those most involved.

Spleen.—The spleen is considerably enlarged, usually to about three times the normal size. It is soft, hyperemic, and may contain necrotic areas. In rare instances an abscess may develop. In addition to the hyperemia there is hyperplasia, with accumulation of a large number of phagocytic cells. Typhoid bacilli may be demonstrated in properly prepared sections. Spontaneous rupture of the spleen is an infrequent complication.

Liver and Bile Passages.—The most marked change in the liver is a parenchymatous degeneration. Small nodular areas of either lymphoid infiltration or necrosis have been described, but are not characteristic of typhoid. Abscess of the liver is rare. Acute yellow atrophy is occasionally observed.

Acute cholecystitis is quite frequent in typhoid. Typhoid ulcers have been reported in the gall-bladder and common duct. These may perforate.

Urinary Tract.—Microscopic examination of the kidney may reveal cloudy swelling with granular degeneration. This is usually most marked in the cortex. In rare instances there may be definite acute nephritis. Multiple abscesses of the kidney are not infrequent. Although large numbers of typhoid bacilli pass through the kidney, pyelitis is rare.

Changes in the bladder are infrequent. Cystitis, considering the great frequency of bacilluria, is very uncommon. More frequently the mucosa shows a mild type of catarrh.

Cardiovascular System.—In conformity with the clinical findings the cardiac lesions in typhoid are confined chiefly to the myocardium. Endocarditis and pericarditis are rare. The former may be caused by the typhoid bacillus, but more frequently by some secondary infection. Pericarditis is apparently never due to infection with the typhoid bacillus. When death occurs late in the disease the heart muscle is flabby and may be markedly mottled by fatty degeneration. The fibers suffer loss of striation and granular and fatty degeneration. Arterial changes are similar to those in other acute infections. The coronary arteries are particularly susceptible. The degenerative changes may take place in either the intima or media. The latter type resembles in many respects the arterial lesions produced experimentally with epinephrin. It is probable that many of the sudden deaths in typhoid are due to these vascular injuries. Changes in a peripheral artery

and arterial thrombosis are rare. Thrombosis in the veins is much more frequent than in the arteries, and is most often seen in the femoral veins, especially on the left side.

Respiratory Tract.—Ulceration of the larynx occurs in 20 to 25 per cent. of fatal cases. Bronchopneumonia was observed in 34 of 105 autopsies at the Johns Hopkins Hospital in Baltimore. It is most frequently due to the streptococcus. Lobar pneumonia, which was found in 8 of the 105, is usually due to the pneumococcus. There is still some doubt as to whether the typhoid bacillus can cause lobar pneumonia. Lung infarcts due to an embolus from a thrombosed vein are not infrequent. Secondary lung abscesses or gangrene may develop.

Nervous System.—Meningitis and brain abscesses due to the typhoid bacillus have been repeatedly demonstrated, but are very rare. Optic neuritis is also seen infrequently. Parenchymatous changes in the peripheral nerves are not uncommon and may be observed when there have been no symptoms of neuritis.

Symptoms.—Incubation Period.—The length of the period between infection and the appearance of the first symptoms is variable. Accurate data upon this point are available because infection has occurred among laboratory workers who knew exactly when the bacilli were ingested. Kisskalt studied 50 cases of laboratory infection and found the usual period of incubation to be fourteen days, the minimum period five days. A girl swallowed a culture of typhoid bacilli with suicidal intent. Headache appeared on the third day, fever on the fourth, epistaxis and rose-spots on the eighth day. Gay reports a case of isolation of typhoid bacilli from the blood on the fifth day. Vincent, on the other hand, describes a case of laboratory infection where symptoms appeared first on the fortieth day. The Commission for the Spanish-American War gave the average incubation period in 780 cases as ten days.

Prodromal Symptoms.—Several days or a week usually elapse before the patient consults a physician. During this period the manifestations are malaise, dull headache, slight general aching, impaired appetite, lack of endurance, drowsiness during the day, and often disturbed sleep at night.

Onset.—Not all patients have the prodromal symptoms. Occasionally the onset is marked by a chill or chilly sensations. This was true in 22 per cent. of the Johns Hopkins Hospital series. *Dull headache* is one of the most constant early symptoms. *Anorexia* is almost invariably marked. *Malaise* and *general aching*, while usually present, do not differ from those of the early stages of other acute infections.

Bronchitis is a very common early symptom. In some epidemics it is present in the majority of cases. In the Johns Hopkins Hospital series it was noted in 25 per cent. of the patients. As these respiratory symptoms may be accompanied by a leukocytosis they may be very misleading from a diagnostic standpoint.

Epistaxis.—Nosebleed is much more common in typhoid than in any other acute infection. It may be a prodromal sign or appear during the early course of the disease. It is due to hyperemia of the nasal mucosa, the cause of which is not known. In the Johns Hopkins Hospital patients epistaxis was present in 21.5 per cent., but in only 6.5 per cent. of Curshmann's cases.

Fever.—The statement is made that the fever curve in typhoid is characteristic. This is true in many but not in all cases. With advancement in diagnostic methods it has been found that there are atypical cases of typhoid that were formerly not recognized, especially the mild types. It is not, therefore, strictly correct to speak of the fever curve of the first and second week as characteristic. Rarely is typhoid afebrile. It is true that typhoid bacilli may be present in the blood of those in contact with the disease without causing any fever. This cannot be considered true typhoid. During epidemics a large number of patients with the prodromal symptoms of typhoid enter hospitals. Although after a few days the symptoms disappear without the development of any of the other characteristic signs of the disease, such as rose-spots, enlargement of the spleen, or positive Widal reaction, the blood of these individuals may frequently be found on culture to contain typhoid bacilli. Even in these mild cases the fever curve may be a miniature of that of the severe type. The form of the temperature curve in the severe cases is, however, far from uniform.

The variations in temperature may be grouped into three parts: First, a step-like rise which ceases at a supernormal level in about one week. This portion of the curve is best observed in a relapse. Second, continuation of the supernormal level usually for ten or fourteen days with only slight daily variation. Finally, a step-like fall to normal within ten days or two weeks. This stage differs chiefly from the step-like rise in that there is greater daily oscillation. The persistence of an evening rise of temperature indicates that the infection has not subsided and increases the probability of a relapse or some complication. The marked daily variation in temperature observed during the decline of the fever is associated with the sloughing of the Peyer's patches, which accounts for the septic character of the curve.

From the so-called typical curve there are many variations. The disease may be ushered in with a chill and the temperature become maximal at once. In rare instances the fever terminates by crisis. In other cases the marked daily variations in temperature during defervescence are lacking. In still others a more or less septic type of fever prevails throughout the disease. This occurs more frequently during paratyphoid than in typhoid fever. As a rule, a chill after the first week suggests the development of some complication, such as phlebitis, cholecystitis, or pneumonia. A sudden drop in temperature during the height of the disease, when not accounted for by hydrotherapy, is suggestive of hemorrhage or perforation of the intestines.

As a rule, the degree of fever is a good index of the virulence of the infection. Patients with severe typhoid rarely have a low temperature.

Pulse.—One of the most suggestive early diagnostic signs of typhoid is the combination of relatively low pulse rate and fever. Many patients pass through the period of maximum temperature with a pulse rate of less than 100. The cause of this bradycardia is not clear; but the condition is apparently not due to stimulation of the vagus, for atropin does not always relieve it. Sudden marked increase in the pulse rate suggests the onset of a complication, such as thrombophlebitis, embolus, pneumonia, perforation of the intestines, or hemorrhage. The development of marked bradycardia during defervescence or convalescence is indicative of myocarditis. From a prognostic standpoint persistent acceleration of the pulse early in the disease is probably indicative of a severe type of infection.

The dicrotic wave is rarely missed in typhoid. It usually appears early and may persist throughout the disease. It is not so constantly present in children as in adults. It may also be absent when there is marked arteriosclerosis. In rare instances the pulse may be tricrotic or polycrotic.

Blood-pressure.—As a rule, the blood-pressure falls quite early in the disease and remains below normal up to and during convalescence. A daily record of blood-pressure may be of value, as certain complications affect it

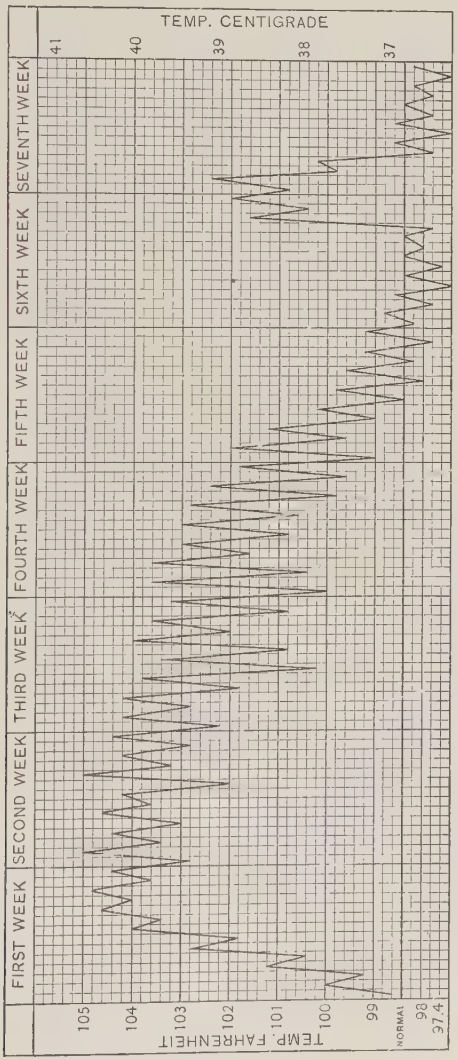

Fig. 3.—Temperature curve in severe typhoid, showing recrudescence late during the sixth week (Anders).

materially. Hemorrhage of moderate degree may reduce the pressure 20 to 30 mm. of Hg. Sometimes following perforation there is a sharp rise in pressure.

Skin.—Roseola.—Toward the end of the first week the characteristic *roseola typhosa* (rose-spots) may appear as a rash of pale red circular spots, standing out distinctly on the white skin, but difficult to detect in the negro.

Their average diameter is 2 to 4 mm. They are slightly elevated and somewhat firmer than the surrounding skin. Not infrequently the central portion is distinctly resistant. They fade on pressure. They are most abundant on the abdomen and chest and next on the back. When very numerous these spots may be scattered over the extremities and even the face. As a rule, a dozen spots on the abdomen is a fair average. In the Johns Hopkins Hospital series rose-spots were present in 93.2 per cent. of the cases. Eichorst reports their constant presence in 2000 cases. They may not develop until defervescence or early convalescence. In some instances they first appear during a relapse. Spots quite similar to rose-spots may be observed in trichinosis, epidemic meningitis, and miliary tuberculosis. The real characteristic of the rose-spot is its crop-like appearance. The average duration of a single crop is three to five days. Rarely are these spots hemorrhagic.

Sudamina, seen more frequently in typhoid than in other infectious diseases, are found in the greatest profusion over the lower abdomen.

Herpes.—Herpetic eruptions are so rare that their presence speaks strongly against typhoid. When present, such lesions usually appear during the first week and are most frequently observed when there are marked respiratory symptoms.

Hair and Nails.—Falling of the hair practically always follows a severe attack of typhoid fever. It is confined to the head; the beard, axillary, and pubic hair is rarely involved. Patients can be assured they will regain their hair. Only in rare instances is there loss of finger- and toe-nails. Transverse grooves or depressions on the new nails are common.

Sweating.—This is unusual in uncomplicated typhoid. The old view that the typhoid patient emitted a peculiar mousy odor has apparently been abandoned.

Tongue.—The lips are usually dry, and both lips and teeth are covered by sordes. In the early stages of the disease the tongue is usually moist and covered with a thick grayish fur. The border, including a triangular area extending up from the tip, is bright red. This type of clean and furred tongue is called the "typhoid tongue."

Abdomen.—Even early in the disease there is often moderate distention of the abdomen, which may be most noticeable in the ileocecal region. There is often tenderness to pressure and a gurgling in the right lower quadrant, which is caused by a mixture of gas and fluid contents in the cecum. Later flatulency may be a distressing symptom. Since the abandonment of the milk diet distention of the abdomen is much less frequent. Moderate abdominal pain is present at some time during the course of the disease in the majority of patients.

Spleen.—The spleen usually becomes palpable by the end of the first week. In no other acute infectious disease is it so uniformly enlarged as in typhoid. In the Johns Hopkins Hospital series the spleen was palpable in 71.6 per cent. of the cases. The edge of the spleen is rounded, soft, and slightly tender.

Stools.—The frequency with which typhoid is associated with *diarrhea* is extremely variable. In the Johns Hopkins Hospital series diarrhea was present in 17.4 per cent., and in the Hamburg epidemic of 1887 in 36.1 per cent. of cases. The diarrhea may be a prodromal symptom or may not develop until the height of the disease. When diarrhea is present the stool

is grayish in color, thin, and has an offensive odor. On standing it separates into a liquid upper and a granular grayish lower layer, thus giving rise to the term "pea-soup stool." It may contain pieces of necrotic Peyer's patches. *Constipation* is much more common than diarrhea.

Urine.—The urine shows the changes characteristic of fever. It is heavy, highly colored, and commonly contains albumin; there is rarely evidence of a real nephritis. Motile typhoid bacilli are often present in the sediment.

The diazo test is positive in about 70 per cent. of cases. With the development of the Widal reaction and the diagnostic importance of blood, urine, and stool cultures, however, the diazo test has lost much of its practical value.

Blood.—The slowly progressive *secondary anemia* usually begins to subside early in defervescence. Marked anemia is much less common since the general use of a liberal diet, and it is rare at present to see an emaciated, anemic typhoid patient.

There may be a slight *leukocytosis* during the prodromal period, especially when there are marked respiratory symptoms. Rarely does the white count exceed 10,000 cells per cubic millimeter. In most cases at the beginning, and in practically all cases at the height of the disease, there is a *leukopenia*. This is due to a reduction in the number of polymorphonuclear cells. There is no apparent relation between this leukopenia and prognosis, except that an increasing leukopenia is usually associated with increasing evidence of toxemia.

Nervous Symptoms.—Dull headache without any characteristic features is common. *Tremor*, especially of the tongue and lips, is frequent at the height of the disease, and may render the speech hesitating and tremulous. *Marked insomnia* may appear early in the disease, but more frequently the patient is drowsy and unable to sleep restfully for any length of time.

Delirium is frequent and may be of such a violent type that the patient requires constant watching. In order to avoid accidents which may be serious, some form of restraint is advisable. The patient is often quite shrewd about attempting to escape, waiting, for example, until the nurse's back is turned, or even striking the nurse or attendant. An alcoholic patient may develop *delirium tremens*.

Body Weight.—Under the old régime when the diet was restricted to milk the typhoid patient rapidly became emaciated. With modern treatment, which permits administration of a liberal diet, extreme emaciation is rare. It has been shown that by forced feeding a typhoid patient can retain approximately his normal weight throughout the disease.

Atypical Onset.—The disease may be ushered in by marked nervous symptoms, such as convulsions or maniacal manifestations. The early meningeal symptoms of severe headache and slight retraction of the neck may lead to confusion in the diagnosis.

Onset with severe bronchitis is very common and typhoid may not be suspected. The leukocytosis which is often associated with this type of the disease may still further mislead the physician.

The onset may be marked by severe vomiting, diarrhea, and abdominal cramps, which suggest some acute intestinal intoxication or infection. Inasmuch as the acute pain may be localized in the right iliac fossa it can easily be mistaken for acute appendicitis. A leukocyte count may be of

assistance in avoiding this error. In some instances the patient is first made aware of the nature of his trouble by hemorrhage or perforation.

Ambulatory typhoid is much more frequent than is usually suspected. During epidemics a large number of patients with slight fever and moderate indisposition continue to attend to their daily duties. On examination they may present all the characteristic manifestations of typhoid. The entire course of the disease may be so mild as to escape detection unless some complication arises. Ambulatory typhoid offers one of the most serious difficulties in controlling the dissemination of the disease.

Typhoid in Infancy and Childhood.—In infants vomiting or convulsions are quite frequently the first evidences of typhoid. Nervous symptoms—especially meningeal in character—are much more common than in adults. The intestinal lesions are usually not so marked, and, consequently, hemorrhage and perforation are less frequent. The mortality is high, and such serious complications as deaf-mutism and arrested development are occasionally observed.

Typhoid in childhood does not differ from that in adults except that it is usually milder.

Recrudescence and Relapse.—All irregular rises in temperature, which are not associated with the reappearance of rose-spots or enlargement of the spleen, may be considered as recrudescences. A relapse, which is practically a repetition of the original disease, may be of very brief duration and may even take place before the temperature has reached normal. For this latter form the term *intercurrent relapse* has been used. A relapse is apparently a reinfection. Although ascribed to a great variety of causes, such as dietetic errors, emotional excitement, and exercise, actual evidence of the influence of any of these factors is lacking. Apparently an inability of the patient to become immune is the underlying cause.

Relapses apparently bear no relation to the severity of the primary disease. The average period of apyrexia between the primary attack and the relapse is about one week, although a period of six weeks has been reported. Relapses are usually milder than the original disease, but they may be more severe. About 4 per cent. of the patients who suffer relapse have two or more. When the disease recurs the intestinal lesions are less marked and, hence, hemorrhage and perforation are less frequent. Relapses occur in slightly less than 10 per cent. of all typhoid patients. They appear to occur more frequently when a high caloric diet is administered.

Complications.—The complications of typhoid, which are the rule rather than the exception, cause 75 per cent. of the deaths.

Hemorrhage.—Gross intestinal hemorrhage occurs in about 7 per cent. of the cases. Its frequency varies in different epidemics and is definitely less when patients receive a liberal diet than when they receive a milk diet. It does not bear any definite relation to the severity of the disease. Occult blood is present in the stools of approximately 30 per cent. of the patients. There may be repeated moderate bleeding or a single severe hemorrhage or all variations between.

This complication appears most frequently during the third week, but may appear during the second week or late in convalescence. A tarry stool or clots of blood are often the first evidence of hemorrhage. If the bleeding is severe the patient may complain of chill or chilliness associated with marked fall in temperature. Pallor, coldness of the extremities, rapid pulse,

and low blood-pressure are usually associated with fairly severe hemorrhage. In addition to the secondary anemia there may be marked leukocytosis. Abdominal pain rarely accompanies hemorrhage; it is not directly due to the bleeding and should always excite suspicion of perforation of the intestines. Distention of the abdomen is not unusual. The prognosis varies for every case. The average mortality is 25 per cent.

Perforation.—Intestinal perforation is the most dreaded complication of typhoid. Its reported incidence varies from 1.5 to 6 per cent.; a fair average is 3 per cent. The perforation is usually single, although 15 have been found at the time of operation and 25 at autopsy. The most frequent site is the lower 18 inches of the ileum, but it may occur in any portion of the large bowel, including the rectum and appendix.

Perforation corresponds to the exfoliation of the sloughs. It occurs most frequently late in the second or during the third week. When there is delay in the healing of the ulcer, it may occur much later, even during convalescence. The immediate determining cause may be increased peristalsis, flatulency, straining at stool, constipation, vomiting, unusual physical exertion, or the irritation of hard pieces of food, including milk curds. The intestines are perforated less frequently when patients receive a liberal diet because of the lessened tendency to flatulency and the absence of milk curds.

Occasionally premonitory symptoms, such as slight pain and tenderness, may be noticed; these are due to areas of local peritonitis over deep ulcers. As a rule, however, the onset is sudden with severe pain, which usually involves the entire abdomen. Patients who are not delirious or stuporous almost invariably complain of this initial pain. It may be constant or paroxysmal in character and may be associated with such symptoms as bladder irritability or frequent micturition; examination of the urine may be necessary to rule out the possibility of renal colic. The pain grows progressively worse and is often increased by change of position or deep breathing.

With the exception of the sudden acute pain and the retching and vomiting that may accompany it, all the signs and symptoms are those of peritonitis. Too much emphasis cannot be placed on the importance of acute abdominal pain as possible evidence of perforation. Acute cholecystitis causes acute pain, but a physical examination demonstrates that in this disturbance the point of greatest tenderness is the gall-bladder region. When the intestines are perforated palpation usually reveals generalized abdominal tenderness and some rigidity, evidence of early peritonitis. Abdominal distention is an inconstant and usually a late symptom. The abdomen may become scaphoid during general peritonitis. Disappearance of the dulness of the liver is inconstant and may be noted without perforation, but is significant when the abdomen is flat. During general peritonitis a friction-rub may be observed, especially over the hepatic or splenic region. The course of the temperature is variable: there may be a sudden rise, a sudden fall, or no appreciable change. As a rule, the pulse rate is raised, but, as this is variable, too much stress should not be laid on it. Only after peritonitis is well developed does the pulse become uniformly rapid and thready. Occasionally there is an early rise in blood-pressure. Too much reliance should not be placed on the leukocyte count because of its extreme variability, but a steady rise following abdominal pain,

provided cholecystitis is ruled out, may be of great diagnostic significance. In some cases an early leukocytosis may disappear. Occasionally following perforation the leukopenia may increase.

The expression may become characteristically pinched and anxious immediately or not until several hours have elapsed. On account of the rapid development of paralytic ileus the bowels rarely move after perforation. Free fluid in the abdomen is a late manifestation. Hiccup may appear early, but is more often a late symptom. Occasionally the peritonitis is due to rupture of a mesenteric lymph-gland. There is not a single sign or symptom pathognomonic of typhoid perforation. The diagnosis must be made by weighing the evidence, constantly remembering that many of the symptoms appear only after the development of a general peritonitis, and that in order to save life we cannot await the appearance of these manifestations. In order to resort to surgical measures sufficiently soon to make the chances of recovery good, it is well to be satisfied with the diagnosis of a probable perforation.

In making the differential diagnosis the possibility of acute appendicitis may be considered, but as both conditions require surgical intervention a laparotomy should be advised. The early symptoms of pneumonia with referred abdominal pain may simulate those of perforation. A definite leukocytosis supports the diagnosis of pneumonia. A careful physical examination and, if doubt still exists, an *x*-ray examination of the chest usually clears up this point. Symptoms of perforation can be simulated by those of a local peritonitis over a deep ulcer. If such a condition is found at operation care should be taken to prevent a later perforation in this area. Thrombosis of the iliac vein may give rise to acute abdominal pain, chill, and leukocytosis.

Thrombosis.—Recognized venous thrombosis occurs in about 2 per cent. of the cases of typhoid. Thrombosis is frequently not recognized, and this fact doubtless accounts for the unexplained sudden, transitory elevations of temperature which may occur during the course of the disease. The condition is recognized most frequently in the femoral veins, especially on the left side, and is due to compression of the left iliac vein by the arterial trunk.

It develops most frequently during or after the third week, about half of the cases occurring during the third and fourth week. In about 30 per cent. of cases it occurs during convalescence. The onset is usually marked by a chill, followed by pain and tenderness in the region involved. When in the femoral vein the tenderness is usually along the course of the vein below Poupart's ligament. In case of iliac involvement the pain may be abdominal. If the thrombosed vein is palpable its cord-like outline can be felt. Edema of the foot and leg may follow femoral thrombosis, the degree of swelling depending upon the degree of occlusion. Leukocytosis is present in about 25 per cent. of cases and the white count may reach 25,000. The chief danger of thrombosis is pulmonary infarction.

Thrombosis of an artery, which is a rare complication, may be followed by gangrene. There is considerable difference of opinion in regard to the cause of thrombosis in typhoid. Injury to the vessel wall is probably the primary factor, although the cause of such injury is not clear. If the endothelium is injured, blood-platelets are deposited and form the nucleus for the thrombus. Thrombosis of the jugular vein is rare and its consequences serious.

Cholecystitis.—Bile, which is antagonistic to many bacteria, is favorable to the growth of the typhoid bacillus. Cholecystitis is, however, relatively infrequent, developing in somewhat less than 2 per cent. of typhoid patients. The onset may be gradual or sudden. It is characterized by pain, tenderness, and muscular rigidity over the involved part. Occasionally a gall-bladder tumor may be palpated. When the onset is sudden the symptoms may readily be mistaken for perforation of the intestines. Chill and vomiting are not unusual. The pulse and respiration may be increased, and a white cell count of 10,000 to 15,000 is not infrequent. Jaundice is an accompaniment in about 30 per cent. of the cases. Cholecystitis may develop at any time during the course of the disease or months after recovery. The typhoid bacilli may remain in the gall-bladder for years and play an important rôle in the formation of gall-stones. The course of cholecystitis is extremely variable. In the majority of cases the symptoms gradually subside. If they persist, however, or recurrent chills appear, drainage of the gall-bladder is necessary in order to avoid perforation.

Abscess of the liver is rare. It occurred only twice in 1500 cases in the Johns Hopkins Hospital series.

Jaundice, except as a complication of cholecystitis, is very infrequent, and is certainly no more common than in other acute infections. It is probably of toxic origin.

Parotitis develops in slightly less than 1 per cent. of all cases of typhoid. It is usually unilateral and non-suppurative in character. The typhoid bacilli may be found in pure culture in the pus. Inasmuch as parotitis usually develops only when the disease is very severe, it may be considered a bad omen. About 35 per cent. of patients with complicating parotitis die. Thrombosis of the jugular vein is one of the serious consequences.

Thyroiditis may be simple or suppurative. It usually involves only one lobe, is an infrequent complication, and is reported to occur more often in individuals with a previously enlarged thyroid gland.

Orchitis appeared as a complication four times in the 1500 cases at the Johns Hopkins Hospital. It usually develops late in the disease or during convalescence, is rarely bilateral, and is suppurative in about 20 per cent. of the cases. The typhoid bacillus, alone or mixed with other bacteria, may be found in the pus.

Mastitis is an unusual complication. It may develop in either sex, but is more frequently seen in the female. It is suppurative in about 50 per cent. of the cases. Typhoid bacilli have been cultured from the pus.

Pancreatitis.—Acute hemorrhagic pancreatitis is rare and usually secondary to acute cholecystitis.

Laryngeal Complications.—Ulceration of the larynx is a rather frequent complication in severe typhoid. It is seen in about 10 per cent. of typhoid autopsies. The usual location is the posterior wall at the insertion of the vocal cords. The typhoid bacillus may be obtained in pure culture from the floor of the ulcer. Hoarseness, aphonia, inspiratory stridor, and blood-tinged mucus are the most frequent clinical manifestations.

Pulmonary Complications.—*Lobar pneumonia* as a complication develops in about 2 per cent. of cases. It may appear early, but more frequently it occurs during the second and third week. In patients who are very ill it may be easily overlooked. The pneumococcus is the more common etiological agent.

Bronchopneumonia is usually a terminal complication and develops with about the same frequency as the lobar type. It is usually of streptococcic origin. Whether either type of pneumonia is ever due to the typhoid bacillus is doubtful.

Pulmonary abscess and *gangrene* are rare complications. They usually follow an infected embolus or aspiration pneumonia, or they develop as metastatic phenomena during general pyemia.

Cardiac Complications.—*Endocarditis* is an infrequent complication of typhoid. It is usually simple, rarely septic in type. The mitral and aortic valves are most frequently involved. Typhoid bacilli have been isolated from the valves in some instances, but, as a rule, streptococci or staphylococci have been found. The soft mitral systolic murmur which is very often present at some time during the course of typhoid fever is, in all probability, due to myocardial involvement of the papillary muscles which prevents proper coaptation of the leaflets. Loud murmurs with dilatation of the chambers are more apt to be of endocardial origin. The diagnosis of mitral endocarditis should be held in reserve until the permanency of the murmur has been established.

Pericarditis is very rare. It may be due to the typhoid bacillus or to pyogenic cocci and may develop at any time during the course of the disease.

Myocarditis.—Involvement of the myocardium is the most frequent cardiac complication in typhoid. Edema of the feet may be the first manifestation, or marked bradycardia, or arhythmia. Rarely the pulse rate is increased. The apex is displaced to the left; the heart tones are faint. A mitral systolic murmur is quite common. Myocarditis is rarely a serious complication. With prolonged rest the myocardium recovers and a complete restoration may be anticipated.

When an individual well past middle life acquires typhoid, *angina pectoris* sometimes develops after recovery. This complication is usually permanent and only rarely permits complete recovery. The condition probably arises from degenerative changes in the walls of the coronary arteries.

Renal Complications.—It is very difficult to decide whether or not a typhoid patient can be said to have *nephritis*. Febrile albuminuria is very frequent, but true nephritis, with the appearance of blood, epithelial, and granular casts in the urine is quite rare. As a rule, the clinical manifestation of nephritis is limited to the urinary findings. Edema or uremia are rarely observed. Patients recover completely from the milder types, but the severe form usually accompanies only severe typhoid, and the mortality, which is high (50 per cent.), is not necessarily due to the nephritis. Rarely does this renal disturbance assume a chronic form.

Pyelitis.—Bacilluria is so common that it cannot be considered a complication. Pyelitis is rare. Chills or irregularity of temperature with pain and tenderness in the lumbar region suggests pyelitis. The presence of pus in the urine may confirm the diagnosis. Complete recovery is the rule.

Cystitis occurred in 2.1 per cent. of the patients in the Johns Hopkins Hospital series. Except when it follows catheterization it is usually caused by the typhoid bacillus. Dysuria, frequent urination, with pus and at times blood in the urine, establishes the diagnosis. Recovery is rapid and complete when the trouble is due to the typhoid bacillus.

Complications in the Bones and Joints.—Bony lesions are troublesome and not infrequent sequelæ. *Periostitis* is the most common. It may appear during the attack or months after convalescence. In the latter case it is usually secondary to a typhoid osteitis or osteomyelitis. The ribs, clavicle, or long bones of the extremities are most frequently involved. The onset is usually not accompanied by temperature changes. The symptoms are redness, pain, tenderness, and swelling over the affected area. When not secondary to an osteitis, recovery is usually rapid, but the disturbance tends to recur.

The typhoid bacillus has a selective affinity for the bone-marrow and may excite an *osteitis* or *osteomyelitis*. Several years may elapse before the lesion becomes sufficiently marked to attract attention. The long bones are most frequently involved. The lesions may be single or multiple. As a rule, the onset is without fever or constitutional symptoms. If pus forms, a sinus may discharge for years. As the typhoid bacillus is usually present in the pus this may render the individual a carrier. In suspected cases *x*-ray examination is of great assistance in making a diagnosis.

Typhoid spine is a term used to describe the pain in the lower dorsal or lumbar region, which often radiates around the body or into the extremities. This trouble appears late in the course of the disease or after convalescence is established. The onset may be sudden, as in acute lumbago, or the pain may gradually increase and become especially noticeable on movement. The spine may become rigid. There may be disturbance of reflexes and weakness of the extremities. Bladder and rectal disturbances have been noted in a few instances. Tenderness along the spine is usually present.

Formerly the typhoid spine was considered a neurosis, and no doubt neurotic symptoms may develop as a result of discomfort. The *x*-ray frequently reveals definite bony exostoses on the vertebræ, which resemble those of chronic osteo-arthritis of the spine. It is highly probable that the "typhoid spine" is a manifestation of spinal arthritis, the radiating pains being due to a pressure neuritis.

The prognosis is good. Recovery is usually complete except when there are marked exostoses, which may cause more or less permanent rigidity of the spine.

Arthritis of the extremities is rare. It may be mono- or polyarticular. Except when it is due to extension from an osteomyelitis it is non-suppurative. Recovery occurs, as a rule, without impairment of function.

Gangrene is rare. When present it is usually due to arterial thrombosis and occurs in the lower extremities.

Pregnancy.—While a patient may pass safely through an attack of typhoid without interruption of pregnancy, approximately 50 per cent. miscarry. Miscarriage increases the chances of a fatal termination. Sacquin states that of 150 cases, 16 per cent. died.

Complications in the Spleen.—Rupture and abscess of the spleen are both infrequent complications. A sudden severe pain in the splenic region with evidence of marked loss of blood is suggestive of splenic rupture. Abscess may give rise to very few symptoms, or to chills, sweats, leukocytosis, and pain in the splenic region. A friction-rub may be heard over the splenic area; or there may be symptoms of diaphragmatic pleurisy, characterized by pain which is intensified on breathing, and is often referred to the region of the left trapezius muscle.

Complications in the Eye.—Serious ocular complications are infrequent. Temporary paralysis of the extrinsic muscles of the eye, probably due to neuritis, may develop during convalescence. Transitory and permanent amaurosis has been reported. Bilateral hemianopsia has occurred and is probably embolic in origin, as it may follow pulmonary infarction.

Complications in the Ear.—Otitis media develops in about 2 per cent. of cases. In stuporous patients with unexplained elevation of temperature it is well to bear in mind the importance of examination of the ear. Furunculosis of the external meatus is quite frequent. Temporary impairment of hearing during the height of the disease is fairly common.

Nervous and Mental Complications.—In addition to meningismus actual meningitis may develop. When suspicious signs or symptoms develop, a spinal puncture should be made. A much increased cell count and globulin content speak for meningitis. Hemorrhage, thrombosis, embolism, encephalitis, and brain abscesses are rare complications. The symptoms are those produced by similar processes of other origin. Pure cultures of the typhoid bacillus may be isolated from a brain abscess. Hemiplegia in typhoid is usually due to thrombosis, rarely to embolism.

Acute myelitis with paraplegia is rare. The first symptoms of insular sclerosis may appear during an attack of typhoid. Bulbar symptoms have been reported.

Peripheral neuritis occurs not infrequently. It may be so severe as to be mistaken for a paraplegia due to lesion of the cord. Tenderness of the toes has usually been considered a manifestation of neuritis. It has been suggested that this trouble may be due to emboli; however, the intense burning and tenderness suggest a neuritis. The plantar surfaces of the toes become so very painful that the patient is unable to tolerate the weight of the bedclothes.

Convulsions are rare and may be due to a variety of causes—toxemia, embolism, thrombosis, or hysteria. Rarely are they uremic. Epileptics are frequently free from seizures during typhoid.

Typhoid Psychosis.—In addition to delirium, which can scarcely be considered a complication, a psychosis develops in about 1 per cent. of cases (Curshmann). This usually disappears during convalescence and rarely becomes permanent. Even the severer types offer a fairly good prognosis.

Diagnosis.—Formerly the diagnosis of typhoid was entirely clinical. At present laboratory tests play a very important rôle. The finding of typhoid bacilli in the blood, urine, or stools when the clinical manifestations are typical is positive evidence of typhoid. The *Widal test*, when positive in a dilution of 1 : 100 in the blood of an individual who has not had a previous attack of typhoid nor received protective inoculation, is indicative of typhoid.

From the standpoint of clinical findings, including history, it is the *syndrome as a whole* rather than any single sign or symptom that has diagnostic value. In any obscure continued fever it is well to consider the possibility of typhoid. The history of malaise, dull headache, slight general aching, drowsiness, and anorexia, with no localized discomfort and negative physical findings is significant, as there are few other acute infections with prodromata which persist for so long. The existence of an epidemic or the history of a recent journey has diagnostic weight.

The combination of persistent high fever with a slow pulse is suggestive.

The dicrotic character of the pulse has less significance. A leukocyte count of 6000 or less is of great importance. Leukopenia may be found in measles, influenza, dengue, malaise, and miliary tuberculosis. With the exception of tuberculosis the differentiation from this group is not difficult. Occasionally in prolonged sepsis (such as septic endocarditis) leukopenia may develop.

Rose-spots have high diagnostic value. Their appearance and distribution, combined with their crop-like occurrence, is distinctly pathognomonic. Enlargement of the spleen is much more common in typhoid than in any of the other acute bacterial diseases. Epistaxis and diarrhea, while suggestive only, are of diagnostic significance when associated with other signs and symptoms of typhoid.

Widal Reaction.—The Widal reaction depends upon a specific substance in the blood of the typhoid patient which has the power to agglutinate the typhoid bacillus. In order to be diagnostic the agglutination should occur when the serum is diluted to at least 1 part in 40. The higher the dilution at which agglutination takes place, the greater the significance of the test. The culture of bacilli should be freshly grown in bouillon or on agar and suspended in bouillon or normal salt solution. The agglutination may be determined macroscopically or microscopically. The latter method can be carried out more rapidly and is more frequently used. The test is made by mixing on a slide freshly grown typhoid bacilli and the properly diluted whole blood or serum. If the test is positive, there is first a loss of motility and then a clumping of the bacteria. The agglutination should be complete within an hour.

The value of the Widal reaction is somewhat limited by its frequently late appearance. It is rarely positive before the end of the first week and may be delayed until the third week; it may not be positive during the course of the disease, but strongly so in the subsequent relapses. A single negative test never excludes the possibility of typhoid. Daily tests should be made until a satisfactory positive reaction is secured. If this method is pursued, about 97 per cent. of patients will give a positive reaction. It is customary to make Widal tests for both typhoid and paratyphoid fever in each case.

With the increasing prevalence of protective typhoid vaccination the diagnostic value of the Widal test has been lessened. The persistence of the reaction after vaccination is extremely variable: in the majority of cases it becomes negative within six to twelve months. In 70 per cent. of the patients who have had typhoid the test becomes negative within seven months (Aldershof). Less than 20 per cent. are positive after one year. A long-continued positive Widal suggests that the subject may be a carrier.

The reaction is rarely positive in high dilution except when the patient has typhoid. It should be borne in mind that it is not infrequently positive in miliary tuberculosis, and that it is reported to be positive without typhoid in icterus. It is possible that in some of these latter cases there exists an old typhoid bacillus cholecystitis. The test may occasionally be positive when autopsy fails to reveal any evidence of typhoid. This is, however, exceedingly rare except when tuberculosis is present.

In addition to the Widal there are other more or less specific reactions, but none of them equal the Widal in accuracy. The more important of these are the *complement-fixation reaction* and the "*Typhoidin*"

reaction, which is a test for localized hypersusceptibility. The latter test possesses considerable value and depends upon local skin or conjunctival reaction to a solution prepared from powdered typhoid bacilli. Its late appearance lessens its value.

Blood-cultures are positive during the first week of the disease in 75 per cent. of the cases. They should be grown in bouillon containing 10 per cent. bile (10 c.c. of blood in 200 c.c. of medium). The fact that blood-cultures are positive during the first week of the disease when the Widal test is negative gives them special value.

Stool cultures are positive in 80 per cent. of cases during the third or fourth week. Typhoid bacilli may be cultured from the urine in 25 per cent. of cases.

The diazo reaction is seldom used because of the greater accuracy of the Widal test.

Differential Diagnosis.—Any prolonged unexplained fever suggests the possibility of typhoid. When the symptom-complex of typhoid, rather than a single sign or symptom, is kept constantly in mind and proper care taken to make frequent cultures and Widal tests, the presence or absence of typhoid infection can usually be determined.

Miliary Tuberculosis.—This may closely resemble typhoid. A history of tuberculosis in the family, or of a previous pleuritis, hemoptysis, or bone trouble is significant. The temperature curve may closely simulate that of typhoid except that there is no step-like fall. The pulse is usually, but not always, rapid in tuberculosis. Cyanosis, cough, persistent lung findings, and cranial nerve involvement are also evidence of tuberculous infection. Meningeal symptoms, which are rare in typhoid, are common in tuberculosis. The findings in the spinal fluid may be of great value in making the diagnosis. Leukocytosis may be absent in miliary tuberculosis, but less frequently than in typhoid. *x*-Ray examination of the chest may demonstrate tubercles. Typical recurrent rose-spots do not develop in tuberculosis. Finally, blood and stool cultures provide decisive data. The Widal test is less reliable, since it may not infrequently be positive in high dilutions during tuberculosis. The writer has recently seen 2 cases of tuberculosis, in both of which there had been repeatedly positive Widal reactions, one of them at a dilution of 1 : 640. Both patients were colored. At autopsy one was shown to have tuberculosis of the suprarenals, the other a general miliary tuberculosis; neither had a history of previous typhoid or protective vaccination. The patient with miliary tuberculosis had a pulse rate of 90, with a temperature of 103° F. and a leukocyte count of 6000. The other patient had a rapid pulse with a temperature of 100° F. and approximately the same leukocyte count.

Subacute Bacterial Endocarditis.—On account of the prolonged fever subacute bacterial endocarditis may be confused with typhoid. The fever is, however, rarely so continuous or so high as in typhoid. Recurrent chills are frequently but not always noted. A history of preceding tonsillitis, sinusitis, or other infection of the upper part of the respiratory tract suggests endocarditis. Bradycardia is rare. A mitral murmur, petechiæ, blood in the urine, or involvement of the joints speak for endocarditis. This is confirmed by finding the *Streptococcus viridans* in the blood. Leukocytosis is usual during endocarditis.

Typhus Fever.—The onset of typhus fever is more abrupt than that of

typhoid and is manifested often by a chill and rise of the temperature to its maximum within two or three days. Delirium appears early. There is marked prostration. The rash develops early, is more profuse, and entirely different in character from the rose-spots of typhoid. The pulse is rapid; the leukocyte count increased. The Widal test and blood-cultures are negative.

Tertiary syphilis may cause prolonged continuous fever. The Wassermann test and other manifestations of syphilis aid in differentiation between this type of fever and that of typhoid. The history of an initial lesion and the character of the rash aid a correct diagnosis.

Trichinosis, when the muscle tenderness is not marked and the patient has a continuous type of fever, may strikingly resemble typhoid. The appearance of rose-spots, resembling those of typhoid, though never appearing in crops, adds to the confusion, but definite leukocytosis and eosinophilia, and the marked muscular tenderness revealed by careful examination are means of differentiation. If in doubt, a piece of muscle adjacent to its tendinous attachment may be removed and examined for the *Trichina spiralis.*

Malaria.—Irregular manifestations of malaria—especially the æstivo-autumnal type—may readily be confused with typhoid. The daily variations in temperature are more marked, the spleen is more enlarged than in typhoid, and the parasites may readily be detected in the blood. The administration of 30 grains of quinin sulphate daily for two or three days determines whether or not the fever is of malarial origin.

Exudative Pleurisy.—A tuberculous pleural effusion may give rise to a continuous type of fever with very few localized symptoms. Dyspnea, rapid pulse, and some cyanosis are usually noted. A pleural effusion can scarcely be overlooked if a careful physical examination is made.

A pleural empyema, which usually causes fever of a septic type, may at times give rise to symptoms resembling those of typhoid. A leukocytosis is not always present. The pulse is rapid and the characteristic findings of typhoid are lacking. Physical examination reveals the true nature of the trouble.

There are some other conditions that may simulate typhoid, such as obscure sepsis, due to pyelitis or osteomyelitis. Not infrequently typhoid fever, early in its course, may be mistaken for acute appendicitis. The diagnosis of typhoid should not be made unless the cultures or the Widal test are positive. Certain signs and symptoms are rarely observed in typhoid—coryza, for example, and sweating and herpes.

Prognosis.—Fifty years ago the mortality rate in typhoid was approximately 20 per cent.; it is now approximately 10 per cent. This change is due in part to the recognition of mild cases and possibly also to lessened virulence. The death rate among negroes is reputed to be twice as high as among whites. Sex makes no difference. The mortality is high in infants and the aged. Among soldiers the mortality is usually low, chiefly because of the age of the patients. During the Spanish-American War the mortality was 7 per cent.; in the American Army during the recent war the mortality was 8 per cent.; in the French Army, slightly over 8 per cent. The average mortality in the Cook County Hospital during the past ten years has been slightly over 14 per cent.

Cause of Death.—Intense toxemia is responsible for one-half the

deaths; perforation, for 15 per cent.; hemorrhage, for 10 per cent.; lung involvement, for 10 per cent. Other complications make up the remainder.

Prophylaxis.—Typhoid is a preventable disease. A good water-supply, as a rule, eliminates serious epidemics of typhoid. The stools and urine of all patients should be disinfected. If it were possible to destroy all typhoid bacilli as they leave the body typhoid fever would be eliminated. Water and milk supplies should be carefully guarded. Oyster beds require inspection. The typhoid patient should be carefully studied after recovery to determine whether he is a carrier. In some cities a permit for handling food is issued by the Board of Health, and all persons seeking positions of this character must secure such a permit. At the first appearance of an epidemic it is necessary that every effort be made to determine promptly its source, and typhoid patients should be isolated and reported to the health officer. The value of immunization against typhoid by vaccination must be publicly emphasized.

Disinfection of Stools and Urine, Hands, and Clothing.—The *stools* should be broken up and treated with a freshly prepared solution of bleaching powder (1 ounce to 1 quart of water). Two pints of the solution should be mixed with the stool and allowed to stand for one hour. Creosol compound (2 per cent. solution), carbolic acid (5 per cent.), formaldehyd (10 per cent.), and bichlorid of mercury (1 : 1000) may also be used. At least 1 pint of such a solution, or a sufficient quantity to cover the stool, must be used. One or 2 quarts of boiling water added to a finely divided stool destroys the bacilli.

Any of the above preparations may also be used to disinfect the *urine*. Some hospitals are provided with sterilizing hoppers where stools or urine and their containers can be treated. Cultures should show the stools and urine free from *Bacillus typhosus* before the patient is freed from quarantine.

The *hands* can be disinfected by scrubbing with soap and water and then with alcohol, 1 per cent. creosol solution, or bichlorid of mercury (1 : 1000). The wearing of rubber gloves is a good safeguard.

The *bed linen*, *towels*, and *clothes* of the patient may be placed in a solution of creosol compound (1 pint to 6 gallons of water), or chlorid of lime (2 ounces to 1 gallon of water), or carbolic acid (3 ounces to 1 gallon of water). They should then be boiled or placed in a bag and immediately sterilized by boiling or steaming. In hospital wards all the utensils used by typhoid patients should be marked and used exclusively for such patients.

Sputum should be collected and destroyed as in tuberculosis. Since typhoid fever is a communicable disease, the patient should be isolated and all those exposed, including members of the family, promptly vaccinated.

Water and Food.—A safe water-supply is the best protection from typhoid. When this cannot be secured, good bottled water may be used, or the water may be boiled for five minutes. House filters rarely offer adequate protection. The use of human excreta for the fertilization of truck gardens should not be permitted, and oyster beds ought never to be located near the outlet of contaminated streams. Food must be protected from flies. Milk can best be rendered safe by proper pasteurization and by inspection of dairies.

Protective vaccination is no longer an experiment, for its value has been demonstrated. During the years 1917 and 1918 in the entire American Army there were only 1058 cases of typhoid, with 158 deaths, while during

the Spanish-American War in an army of 107,973 soldiers there were 20,738 cases of typhoid. Not all of this improvement can be ascribed to preventive vaccination, because better sanitary conditions were an important factor.

A triple vaccine is now generally used. Each cubic centimeter contains 1,000,000,000 typhoid bacilli and 750,000,000 each of paratyphoid *A* and *B*. The first dose is 0.5 c.c., the second and third, 1 c.c. each. The dose for children should be determined by their weight. The injections are subcutaneous, not intramuscular, and, according to Gay, may be given at one- or two-day intervals. Formerly an interval of a week was always allowed between doses. There may be no reaction following the injection, but usually there is some fever, headache, and general aching. Only rarely is there nausea or vomiting. If a severe chill develops within an hour after the injection the vaccine has probably been introduced into a vein. Reactions are less liable to appear in children than in adults, and are apt to follow physical activity after inoculation. In order to avoid a reaction it is well to give the injection just before the patient goes to bed; if the vaccine is administered during the day, quiet during the remainder of the day is necessary.

The protection given by vaccination is not absolute. An overwhelming infection may break down the barrier, but when a protected individual does acquire typhoid the disease is apt to pursue a mild course. It is claimed that the death rate among vaccinated individuals is only one-fifth that of the unvaccinated. The vaccination should be repeated every three years in order to insure a high degree of protection. In case an epidemic develops, revaccination should be advised, even if the time elapsed has been less than three years. After vaccination there is no evidence of an increased predisposition to other infections.

Treatment.—The typhoid patient should be isolated and the health authorities notified. When possible a trained nurse who has been instructed as to the methods of dissemination of the infection should be in attendance in order to lessen the danger of transmission to other members of the family. She should thoroughly understand the disposal of excreta, care of bed-pans, urinals, hands, food utensils, and bedding. In addition to instruction as to the best means of avoiding infection, vaccination should be insisted upon. If the patient remains at home, the entire family must be vaccinated, and the sick-room should be kept free from flies by screens, fly-paper, and swatters. When possible it is advisable to transfer the patient to a hospital. Isolation is in this way simplified, danger to other members of the family is lessened, ready access to the laboratory assures prompt service, and complications, such as perforation or hemorrhage, can be handled much more efficiently.

The nurse or attendant should be instructed in regard to the symptoms of perforation and hemorrhage, and should report to the physician any new sign or symptom, especially acute abdominal pain, tympanites, hiccup, or sudden change in temperature or pulse. With the first evidence of delirium a foot restraint must be applied, as the patient may escape through the window even when the attendant is present. A rubber sheet should be placed next to the mattress in order to avoid soiling with urine and feces. After each feeding the teeth and mouth should be cleansed. The skin needs to be kept clean by frequent bathing; alcohol may be applied several times daily to the buttocks and sacral region. If the bowels do not move, an enema

must be given. There is no objection to the use of liquid petrolatum as a laxative, but purgatives should be avoided, as they may excite diarrhea or be a factor in bringing about perforation.

Diet.—Since the fever is prolonged, it is essential that the patient be adequately nourished in order to prevent extreme emaciation. The greatest advance in the treatment of typhoid has been the adoption of the high calory diet. Milk curdles on reaching the stomach, and thus by becoming semisolid increases the consequent danger of trauma to the intestinal ulcer. The curds may undergo bacterial decomposition in the intestine and give rise to tympanites which predisposes to perforation. The patient soon tires of a strictly milk diet and refuses to take an adequate amount of food. An examination of the records of typhoid patients at Cook County Hospital during the time when a strictly milk diet was used showed an average daily consumption of less than 1 quart, *i. e.*, the patients received less than 650 calories daily.

It has been estimated that during the height of typhoid fever a patient consumes half a pound of muscle daily. This protein consumption can be avoided by the administration of proper food. Coleman and Shaffer were the first to show that it was possible to carry a patient through typhoid fever without loss in weight. The average patient, provided he is not delirious, will eat, even at the height of the fever, if given something he relishes. With the present method of liberal feeding the anemic, emaciated convalescent is rarely seen, and convalescence is definitely shortened.

The administration of a liberal diet has actually lessened the mortality. Deaths from toxemia, hemorrhage, and perforation are less numerous. Coleman reported two series of typhoid patients, one treated with a milk diet, the other with a liberal diet. The mortality on the high calory diet was 8.1 per cent. and on the milk diet 17.6 per cent. Perforation developed in 0.9 per cent. of the patients on liberal diet and in 3.15 per cent. of those on milk diet; hemorrhage in 9.4 per cent. on the liberal diet and 14.4 per cent. on the milk diet. It is generally recognized that relapses are more frequent when the diet is liberal. No satisfactory explanation of this is offered. Coleman states that relapses occurred in 18 per cent. of those on the liberal diet and 14.9 per cent. of those on the milk diet. Tympanites was present in 17.6 per cent. of the individuals on the liberal diet and 31.5 per cent. of those on the milk diet. Both delirium and stupor are reported to be less frequent since the high calory diet has been used.

The foods selected should be soft and highly nutritious. As carbohydrates protect the burning of the body protein, they should be given freely. Fats have a high food value and ought, consequently, to provide about one-third of the total calories. An adequate amount of protein is contained in almost any diet furnishing a sufficient number of calories. An attempt should be made to administer 3000 calories daily. Of this number, more than half should be derived from *carbohydrates*, and it is, therefore, necessary to give large amounts of sugar, either as such or in the form of jellies, jams, marmalades, and strained honey. Lactose has the same food value as ordinary sugar, but, as it is not so sweet, can be employed in larger amounts. It may be used on cereals and especially in lemonade; 100 grams of lactose ($3\frac{1}{3}$ ounces) may be added to a glass of lemonade without rendering it distasteful. There is no objection to permitting patients to take their sugar in the form of syrup or candy. Only in case of marked flatulency may it be

necessary to reduce the amount of sugar. The *fats* can be given in the form of butter and especially cream. The dry breakfast foods take up a very large amount of cream, and cream soups, cream toast, egg-nogs, and ice-cream also provide a means of preparing cream in appetizing ways. When diluted with charged water cream is a very palatable drink. In case of diarrhea it may be necessary to restrict fats. The *protein* is supplied by eggs, milk, and cream. Egg-nogs or malted milk may be given between meals.

Many of the simple desserts, like rice pudding, custard, prune whip, tapioca, and gelatin, when cream is added, have a high food value. Coffee with cream may be taken in moderation. Chocolate and cocoa are nutritious. In addition to these concentrated foods, for the sake of variety, a patient may take purée of green vegetables or baked and mashed potatoes. There is no objection to well-toasted bread.

It is not necessary to determine accurately the number of calories. The patient may have all the food he will take. As it is important to vary the daily dietary in order to tempt the patient's appetite, adherence to a special daily diet is inadvisable. The following list may prove helpful in arranging attractive menus:

Food.	Quantity.	Caloric content.
Cream, 20 per cent	250 c.c. (½ pint)	600
Cream soup	4 ounces	125
Egg	1	75
Sugar	1 ounce	120
Oatmeal with cream	1 tablespoonful	125
Cream toast	2 slices	300
Mashed potato	1 tablespoonful	60
Butter	1 ball	120
Dry toast with butter	1 slice	120
Jelly	1 tablespoonful	110
Egg-nog	1 glass, with 1 heaping tablespoonful of sugar	250
Egg lemonade	1 glass, with 2 heaping tablespoonfuls of lactose	250
Chocolate pudding with cream	1 tablespoonful	200
Custard	2 tablespoonfuls	75
Ice-cream	2 tablespoonfuls	175
Cocoa	1 cupful	275
Milk	1 glassful	150

The following daily outline is given merely as a suggestion:

	Calories.
Cream soup, 4 ounces	125
Mashed potato, 2 tablespoonfuls with butter	120
Oatmeal, 1 tablespoonful with cream, 2 ounces	200
Eggs, 2	150
Cream toast, 2 slices	300
Dry toast (2 slices with butter)	240
Egg-nog, 2 glasses, with 1 tablespoonful sugar in each	500
Egg lemonade, 1 glass, with 4 tablespoonfuls lactose	370
Chocolate pudding, 2 tablespoonfuls	200
Ice-cream, 2 tablespoonfuls	175
One glass milk and cream, half and half	275
Cup cocoa	275
Total	2930

The use of advertised prepared foods should be discouraged. They are expensive and not to be compared in food value to cream and eggs.

Treatment of the Fever. — There is an increasing tendency to consider fever *per se* as a beneficial phenomenon which facilitates the develop-

ment of immunity. Experimental work suggests, however, that extremely high temperatures (104° F. or above) are harmful and should be controlled.

The use of *drug antipyretics* has always been considered objectionable. The Brand method of reducing fever by hydrotherapy is gradually being abandoned or modified. This consists in placing the patient in a bath-tub containing water at a temperature of 75° to 80° F. After a few minutes the bath is further cooled to 70° F. by the addition of ice. A cold wet towel is applied to the patient's head and vigorous friction of the skin is maintained during the entire period in the tub—for fifteen to twenty minutes. The patient is then placed in bed between hot blankets and given hot drinks. This procedure is repeated every three hours provided the temperature is as high as 102.2° F.

Hydrotherapy is now employed in typhoid to stimulate the patient and increase his feeling of well-being. Except in hyperpyrexia its object is not primarily to lower the temperature. For this purpose tepid water or alcohol and water may be used. The condition of the patient rather than the temperature is an index of the need of bathing. The restless or stuporous patient may be definitely improved by tepid baths, which may be repeated whenever necessary. For temperatures of 104° F. or above more vigorous methods may be used, such as cold packs or cold sponges, with vigorous rubbing in order to bring the blood to the peripheral vessels.

Drugs play a very unimportant rôle in the treatment of uncomplicated typhoid. The use of intestinal antiseptics has been abandoned. Antipyretics are now condemned. Hexamethylenamin, in 0.5 to 1 gm. ($7\frac{1}{2}$–15 grains) doses three times daily, may be given after the second week for the purpose of preventing or combating bacilluria. As the urine in typhoid is usually strongly acid it is not necessary to give drugs to increase this acidity and thus facilitate liberation of formaldehyd. Hexamethylenamin is of no value in cholecystitis on account of the alkaline character of the medium. Except when patients are addicted to alcohol there is no indication for its use.

Vaccine and Serum Therapy.—Subcutaneous vaccine therapy in typhoid has been largely discontinued. The results apparently did not warrant its continuance. When typhoid vaccine is given intravenously in amounts sufficient to excite a chill the disease terminates by crisis in about 20 per cent. of cases. This effect is caused not by a specific, but by a foreign protein action. The reaction is so violent that this form of treatment cannot be recommended on account of the danger of exciting intestinal hemorrhage. Holler has used small doses of foreign protein intravenously—just enough to excite a slight temperature reaction—and reports a mortality of 0.5 per cent. in a series of 350 cases. The further development of this treatment should be followed.

The value of specific serum therapy has not been demonstrated.

Treatment of Special Conditions.—*Constipation* is less frequent when the diet is liberal. It should be treated by daily enemas or liquid petrolatum. Cathartics should not be used.

Diarrhea is rarely troublesome. An attempt should be made to correct it by eliminating jellies, sugar, cooked fruits, and cream from the diet. A diet of scalded milk will often give relief. Opium should, if possible, be avoided on account of the marked flatulency that may follow sudden checking of the bowels. Bismuth subnitrate (2 grams—30 grains) every three hours

or mistura cretæ (15 to 30 c.c.—½–1 ounce) every three hours, or bismuth salicylate (0.7 gram—10 grains) every three hours may be tried. When the bowel movements are not controlled by simple measures opium may be used.

Flatulency is less troublesome since the strict milk diet has been abandoned. Jellies, lactose, and cooked fruit should be omitted if it develops. The bowels should be kept moving freely with enemata. A turpentine stupe is a traditional remedy of questionable value—turpentine 4 c.c. (1 dram) to hot water 1 liter (1 quart). Drugs to increase intestinal peristalsis, as eserin and pituitrin, should be avoided. As flatulency predisposes to perforation, the onset of acute abdominal pain in flatulent patients should excite suspicion.

Toxemia.—Our present knowledge of toxemia indicates that the best method of treatment is to increase the fluid output. Fluids should be given by mouth, or in case the patient is delirious or comatose, by rectum, or subcutaneously, or intravenously. Alkaline diuretics may increase the diuresis. If the patient will not swallow, a 5 or 10 per cent. glucose solution should be administered intravenously. This will furnish some nourishment and lessen the acidosis of starvation.

Perforation.—The treatment of perforation is immediate operation, and must frequently be undertaken on a doubtful diagnosis. If possible, the operation should be performed under local anesthesia. The average mortality of 65 to 70 per cent. may be lowered by early diagnosis and prompt operation.

Hemorrhage.—After hemorrhage all food by mouth should be withdrawn. Sufficient water may be given by mouth to quench thirst. To enforce absolute rest an ice-bag or coil may be placed on the abdomen. In order to retard peristalsis and enforce quiet morphin should be given hypodermically. Objection has been made to the administration of morphin on account of the danger of masking a perforation which may develop simultaneously with the hemorrhage. While this double complication occurs occasionally, it scarcely warrants withholding a valuable therapeutic agent like morphin. The use of styptic or astringent drugs by mouth is valueless and may excite nausea. The same is true of vasoconstrictor drugs, like adrenalin, pituitrin, and ergot. The use of adrenalin or pituitrin subcutaneously may do harm by raising the blood-pressure. Emetin subcutaneously should be avoided. Calcium chlorid, on account of its reputed value in facilitating coagulation, may be given in doses of 1 gm. (15 grains) three or four times daily. A subcutaneous injection of 30 to 40 c.c. of fresh blood is of greater value in aiding coagulation; on account of its harmlessness it is more desirable than horse-serum or other protein products which increase blood coagulation, and is, furthermore, immediately available.

Transfusions with normal salt solution or blood should only be undertaken if the patient's condition becomes critical, as a low blood-pressure favors plugging of the bleeding vessels. The quantity of fluid transfused should be moderate and the flow should be very gradual in order to reduce to a minimum the chances of raising the blood-pressure. Feeding may be started gradually after the bleeding has ceased. No attempt should be made to secure a bowel movement until forty-eight hours after the end of the hemorrhage, as determined by hemoglobin and red cell count, unless flatulency develops; an enema should then be given.

Cholecystitis.—As a rule, surgical interference is not necessary for cholecystitis. The mild cases subside after a few days. An ice-bag or heat may be applied to relieve pain. The patient should be watched and frequent leukocyte counts made. If the pain, tenderness, or evidence of sepsis becomes progressively more marked, surgical treatment is advisable. If the pain is intense, morphin should be given. Drug treatment to disinfect the gall-bladder is valueless.

Phlebitis.—The use of citrates as a preventive of phlebitis is of theoretical rather than practical interest. The extremity which is involved should be elevated, kept warm, and held at rest. Rarely is the pain sufficiently severe to require sedatives. Absolute rest should be maintained for two weeks in order to allow the thrombus to become fixed. After recovery it is often advisable to apply an elastic support.

Morphin is necessary to relieve the pleural pain and allay the patient's apprehension during pulmonary embolism.

Bone Lesion.—The pain from a periostitis is usually not severe and can be partially relieved by local application of heat or cold. Bone lesions should be examined under *x*-ray and carefully watched for evidence of suppuration.

Typhoid Spine.—It is the rule for patients to recover from typhoid spine. When the pain is severe it may be controlled by heat, salicylates, or immobilization. When marked osteo-arthritis is shown by the *x*-ray, complete recovery is improbable. The treatment is the same as that for osteo-arthritis from other causes.

Myocarditis.—If myocarditis develops, rest until the heart muscle is restored is essential. This should be followed by gradually increasing exercise in order to determine the functioning power of the heart. Digitalis is rarely necessary. If the patient is kept sufficiently quiet to avoid dilatation, complete recovery may be anticipated.

Orchitis, Parotitis, and Thyroiditis.—An ice-bag may be applied to relieve the pain of orchitis, parotitis, and thyroiditis. With the first evidence of suppuration drainage should be employed.

Bacilluria.—Hexamethylena minin 0.7-gm. (10-grain) doses three times daily is beneficial for patients with bacilluria. If the urine is not strongly acid, sodium acid phosphate, 1 gm. (15 grains) three times per day, will increase the urinary acidity and permit the liberation of formalin.

Carriers.—The treatment of carriers is far from satisfactory. Without treatment the typhoid bacillus may disappear from the stools for months, and then reappear. It is, therefore, difficult to determine when an individual is actually cured. Cholecystectomy cures some cases, and its advisability may be discussed with the patient. Inasmuch as a permanent cure cannot be assured, the operation should not be too strongly urged. Vaccine therapy has also been recommended. The most important part of the treatment is the education of the patient. He should be taught cleanliness and should not be permitted to become a food handler. A patient cannot be said to be cured until frequent negative stool cultures have been obtained during a period of at least six months.

Skin.—Frequent bathing and change of posture is of value in preventing bed-sores. In addition, alcohol should be applied to the parts subject to unusual pressure. If a bed-sore develops, a ring or air-cushion will relieve pressure. The ulcer should be kept clean and zinc ointment applied daily.

Convalescence.—Restriction of the diet may cease when the pa-

tient has been without fever for two weeks. When the temperature approaches normal the patient may be allowed to sit propped up in bed. Within a few days after he becomes fever free he may sit in a chair. He may then be permitted to walk, gradually increasing his daily exercise until his strength approaches normal. Then, provided he is not a carrier, he may resume his occupation.

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PARATYPHOID FEVER

Definition.—Paratyphoid fever is an acute general infection with the paratyphoid bacillus *A* and *B*, characterized by the same clinical signs and symptoms and pathological changes as typhoid fever.

Incidence.—Until the Great War paratyphoid fever was considered as a comparatively rare disease. In 1910 only 1000 cases had been reported in the literature, and these were chiefly paratyphoid *A*. The majority of these had been observed in Germany. With protective inoculation in the French and English Armies limited to typhoid fever during the early part of the World War, investigation of the disease of the inoculated soldiers revealed the great prevalence of paratyphoid fever. In 1916 the American troops on the Mexican border, while protected only against typhoid, suffered severely from paratyphoid. As the American Expeditionary Force was inoculated with both typhoid and paratyphoid there was a total of only 170 cases of paratyphoid among our soldiers overseas. In Gallipoli the incidence of typhoid was only 7 per cent. as compared with 93 per cent. of paratyphoid. Paratyphoid *A* was the prevailing type on the Mexican Border. In Gallipoli paratyphoid *B* was the prevailing type at the beginning; later it was almost entirely replaced by type *A*.

Etiology and Bacteriology.—Typhoid and paratyphoid are distinct diseases. An attack of typhoid or protective vaccination against typhoid does not confer immunity to paratyphoid.

Archard and Bensuade in 1896 were the first to isolate the paratyphoid *B* bacilli from the blood and dejecta of patients. The first reported epidemic occurred in Saarbrucken, Germany, in 1902. Since that time the micro-organism has been detected in food and water supplies, its distribution being similar to that of the typhoid bacillus.

The paratyphoid bacillus *A* was first isolated from the water-supply of an Italian village in 1903 by Paladino-Blandino.

Bacillus paratyphosus occupies an intermediate position between *Bacillus typhosus* and *Bacillus coli*. The paratyphoid bacillus *A* is more closely related to the typhoid bacillus. *Bacillus enteritidis* belongs in the same group,

and is a frequent cause of the food poisonings which have not infrequently been mistaken for paratyphoid fever.

Bacillus fœcalis alkaligenes is also closely related, and can give rise to symptoms (including perforation) closely resembling those of typhoid and paratyphoid. The writer has seen one case of infection with this micro-organism where the disease in many respects simulated typhoid. The fever was more septic in type and there was a decided leukocytosis. The pulse was rapid and rose-spots did not appear. Blood-cultures and the Widal test were both negative. The patient developed a perforation and at operation the bowel presented the typical appearance of typhoid. Paratyphoid is disseminated in the same manner as typhoid; that is, chiefly through water, food, and carriers. The resistance of the micro-organism to external agents is the same as that of the typhoid bacillus. In animals *Bacillus paratyphosus A* is much less virulent than *B. paratyphosus B.*

Cultural Qualities.—The cultures of the *Bacillus paratyphosus* when grown on Endo, Conradi-Drigalski, or malachite green media cannot be distinguished from those of *Bacillus typhosus*, but can readily be differentiated from colonies of the colon bacillus. The paratyphoid group is differentiated from the typhoid first by its much greater power to ferment certain sugars, especially maltose, glucose, and levulose. *Bacillus paratyphosus B* may be differentiated from *Bacillus paratyphosus A* by its characteristic production of alkali in milk. There is first a slight acidity followed by an alkaline reaction due to the formation of ammonia. Media containing the subacetate of lead is blackened by the *Bacillus typhosus* and the *Bacillus paratyphosus B*, but not by the *Bacillus paratyphosus A*. Type *B* ferments xylose; type *A* does not.

The agglutination test, when properly applied, furnishes a reliable means of differentiation. Specific antiserums can be prepared by immunizing rabbits with each type. Agglutination in dilutions of 1 : 1000 of the serum identifies the type.

About 10 per cent. of patients with typhoid give a positive agglutination reaction to one or both paratyphoid types. The serum of a patient with paratyphoid *A* may occasionally agglutinate *Bacillus paratyphosus B.*

Morbid Anatomy.—There is little difference in the pathology of typhoid and paratyphoid. Intestinal lesions are less constant during paratyphoid fever, and the large intestine and appendix are apparently more frequently involved than in typhoid.

Symptoms.—The incubation period varies from three to fifteen days. Clinically it is impossible to differentiate between typhoid and paratyphoid infection. The two types of paratyphoid present much the same clinical manifestations. As *Bacillus paratyphosus A* is very closely related to the *Bacillus typhosus* the clinical manifestations are very similar. The *Bacillus paratyphosus B* approaches in its character the colon bacillus, and the onset of the infection is more frequently acute and marked with gastro-intestinal symptoms.

The differential diagnosis of typhoid and paratyphoid depends upon laboratory tests and not on signs and symptoms.

That paratyphoid is a milder infection than typhoid is shown by its shorter duration and lower mortality. The onset, as a rule, is more rapid, frequently with chill or vomiting, abdominal pain, and diarrhea. At the time of onset it can readily be mistaken for food poisoning. Diarrhea is

present in more than half of the cases. Early vomiting is present in about 50 per cent. of cases. Severe headache is much more common in paratyphoid than in typhoid. Herpes of the lips, so rare in typhoid, is not infrequent in paratyphoid.

The temperature rises rapidly at the onset and may reach its maximum in forty-eight hours. The fever curve is similar to that of typhoid, except that it shows a more marked daily variation and a not infrequent termination of the fever by rapid lysis. The average duration is two or three weeks.

Profuse perspiration, which is rare in typhoid, is very frequent in paratyphoid and probably accounts for the wide daily variation in temperature.

Complications.—All the complications of typhoid may occur in paratyphoid. In 1917 Webb-Johnson studied the incidence of complications in 344 paratyphoid *A* cases and 1038 cases of paratyphoid *B*. *Hemorrhage* was noted only once in the paratyphoid *A* group and fifteen times in type *B*. Perforation developed once in the *A* group and three times in the *B* group. A considerable number of the group had received protective inoculation. This should be taken into consideration, as these two complications were much less frequent in the inoculated. On account of lack of statistics the frequency of other complications cannot be determined with any degree of accuracy. *Lung* complications are reported more often. *Splenic abscesses* are also thought to occur with greater frequency.

Relapses and recrudescences appear with the same frequency as in typhoid.

Diagnosis.—Characteristic cultural peculiarities plus the results of the agglutination test assure correct diagnosis. At the onset paratyphoid is most frequently mistaken for food poisoning. This possibility can be ruled out if the fever continues more than two or three days.

Prognosis.—The mortality is lower than in typhoid. Before the War the mortality was 1.5 per cent. in 2725 reported cases; during the War in a series of 2118 cases in France the mortality was 1.3 per cent. There were only 3 deaths in the 170 cases which developed in the American Expeditionary Force. In Mesopotamia, however, the mortality was high—10 per cent. In some of the hospitals in France the death rate among patients with paratyphoid was greater than that among those with typhoid. This, however, is exceptional.

The chief causes of death are pneumonia, hemorrhage, and perforation.

Treatment.—The treatment, both preventive and active, is the same as for typhoid fever.

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COLON BACILLUS INFECTIONS

The *Bacillus coli* is widely distributed in nature and has been isolated from air, water, and soil. It is almost constantly present in the intestinal

tracts of man and some of the higher mammals. In the large intestine it may be present in almost pure culture. It is commonly found in the genitalia of women and may occur in vaginal discharges. It is frequently present in puerperal infections.

In the intestinal tract of man it is usually a harmless parasite. When it invades other structures, either alone or in conjunction with other bacteria, it may be responsible for serious pathological changes. On account of the common occurrence of agonal or *postmortem* invasion of the body by the colon bacillus its presence in organs at autopsy has little significance.

The *Bacillus coli* is the most common bacterial cause of pyelitis and cystitis. It is frequently present in cholecystitis. Serious colon bacillus septicemia may develop as a complication of pyelitis or colon bacillus abscesses.

Meningitis has been reported to be caused by the colon bacillus, and colon bacillus pneumonia has been reported as a complication of a generalized infection. The bacillus has been considered by some to be the etiological factor in hemorrhagic septicemia of the newborn.

Colon Bacillus Cystitis and Pyelitis.—The colon bacillus is the most frequent cause of infection of the urinary bladder and pelvis of the kidney. It is present in cystitis in almost 50 per cent. of cases and in 20 per cent. in pure culture. It is reported to be responsible for 80 per cent. of the infections of the pelvis of the kidney. In addition to producing inflammatory processes in the urinary tract, the colon bacillus is a frequent cause of bacilluria.

The channel through which the infection reaches the pelvis of the kidney is still open to discussion. In man organisms very frequently pass into the urine from the blood-stream. If the drainage through the ureter is interfered with, pyelitis may develop. Impaired drainage is a very important factor. When the pyelitis is secondary to a cystitis the infection travels through the lymphatics in the mucosa and submucosa of the ureter. It is questionable whether the infection ever spreads by direct extension up the lumen of the ureter. The right kidney is more frequently involved than the left, a fact which is explained by passage of the infection through the network of lymphatics connecting the hepatic flexure of the colon with the kidney.

Occasionally colon bacillus infection of the pelvis of the kidney follows marked intestinal disturbances with either diarrhea or stubborn constipation. Female infants or young children are prone to develop pyelitis. Primary pyelitis is much more common in females than in males. The symptomatology and treatment of pyelitis are discussed in the chapter on this subject.

Colon bacillus infection of the bladder may be due to instrumentation, foreign bodies, retention of urine for any cause, or it may be secondary to pyelitis. It is claimed that the colon bacillus is present in the urethra in 20 per cent. of healthy women. Infection of the bladder may be of hematogenous origin. Extension through the lymphatics from the vagina or rectum is a possible but probably unusual method of infection.

Colon Bacillus Septicemia.—General infection with the colon bacillus probably occurs much more frequently than is recognized. It is overlooked in the majority of cases because the symptoms are ascribed to the primary focus. Before the diagnosis of colon bacillus septicemia can be certain the *Bacillus coli* must be obtained from the blood during life.

The focus responsible for the generalized infection is located most frequently in the genito-urinary tract, intestinal tract, or gall-bladder. The

onset is marked by a chill, followed by a septic type of fever with leukocytosis of varying degree. Jaundice is not infrequently present. In some cases the condition may easily be mistaken for typhoid. Metastatic infections due to colon bacillus septicemia are, on the whole, infrequent when compared with pneumococcus or streptococcus sepsis.

The intravenous use of mercurochrome, as recently recommended, is dangerous. The results reported are probably due to the reaction and not directly to the drug. This method of treatment cannot be recommended.

Cholecystitis.—According to Naunyn the colon bacillus is responsible for 80 per cent. of the infections of the gall-bladder. The infection is supposed to take place through the blood and lymph channels and not by direct extension up the common duct.

Colon bacilli are able to decompose the bile salts and cause a precipitation of cholesterin, thus furnishing the nucleus for calculus formation.

Gall-stones have been produced in animals by infecting the gall-bladder with *Bacillus coli*.

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BACILLARY DYSENTERY

Definition.—Bacillary dysentery is an infectious disease, usually acute, sometimes chronic. It is caused by a genus of bacilli of which there are two important species and some related varieties, and is characterized clinically by the frequent passage of stools containing mucus, pus, and blood, accompanied by abdominal pain and tenesmus; and pathologically by an acute diffuse inflammation of the large intestine which leads to necrosis of the mucous membrane. It occurs endemically in certain parts of the world, especially in the tropics, and is liable to develop in epidemics under certain conditions.

History.—Hippocrates applied the name "diarrhea" to the frequent passage of liquid stools, and "dysentery" to the passage of bloody stools. Galen and other ancients gave the term its present connotation by making it include tenesmus and the passage of stools containing mucus. The disease can be traced in various historic epidemics, especially in wars.

The bacteriology of dysentery was conclusively established by Shiga (1898) Kruse (1900), and Flexner (1900). The disease, which was one of the most important of the Great War, first broke out in Gallipoli in 1915 and was responsible for a high proportion of the 120,000 casualties from sickness in that area. The expert research during the war has greatly increased our knowledge of the malady and has proved especially helpful in diagnosis. The results of the studies by British workers have been summarized by Manson-Bahr in *The Official History of the War.*

Incidence.—DISTRIBUTION.—Dysentery has occurred in every part of the world, but conditions are most favorable to its propagation in tropical and subtropical climates. During the Great War it prevailed on every front.

Rogers' statistics show that the incidence of amebic as compared to that of bacillary dysentery increases as the equator is approached.

Age and Sex.—Individuals of all ages are subject to dysentery, but it is most common in men between twenty and thirty and in children under two years of age.

Hygiene.—Lack of sanitation and the crowding together of large numbers of human beings are the most important determining factors in the incidence of epidemics, as, for instance, in camps, lunatic asylums, and jails.

Etiology.—The predisposing causes are (1) bad sanitation, and (2) factors liable to impair the resistance of the individual, such as chilling, enervating tropical heat, want and privation, severe physical exertion, and irritation of the intestines by coarse or indigestible food. The rôle of flies as carriers has been emphasized by Manson-Bahr and J. F. Taylor. Dysentery bacilli live for several days in the fly's intestine. Contamination of food and water is an important source of infection.

Bacteriology.—"The bacilli credited with the causation of dysentery all belong to a natural genus which presents the following characters: They are short rods, destitute of flagella and non-motile, forming no spores, not liquefying gelatin, negative to Gram's stain, and fermenting glucose and sometimes other sugars and alcohols without the formation of gas" (Andrewes and Inman).

The bacillus discovered by Shiga (1898) and again isolated by Kruse (1900) is now regarded as a species distinct from that isolated by Flexner (1900) and the types related to it, classified by Hiss (1904) as the "Flexner," "Strong," and "Hiss-Russell" or "Y" bacilli. The latter are distinguished from Shiga's bacillus by the fact that they ferment mannite. The species are serologically distinct. Shiga strains are all agglutinable by Shiga serum, while the mannite-fermenting bacilli are not. The latter form a group of five races called *V*, *W*, *X*, *Y*, *Z*, which are related by the production of group agglutinins, but differentiated from each other by the higher agglutination titer of their immune sera toward homologous strains than toward the others. This serological classification has superseded that made by Hiss on the basis of sugar fermentation. Shiga's bacillus produces both an exotoxin, which acts specifically on the central nervous system, and an endotoxin, which selectively affects the mucous membrane of the large intestine.

Morbid Anatomy.—The early lesions in mild cases have rarely been observed, but they are described by Manson-Bahr as commencing in the lymphoid follicles of the colon. The superficial layers of mucous membrane are scattered over with small dots of inflammatory exudate. The mucous surface rapidly becomes diffusely inflamed; in the very acute cases bright red and hemorrhagic. This inflammatory reaction to the toxin progresses until the mucous layer undergoes coagulation necrosis and is converted into a false membrane. Microscopically Lieberkühn's follicles may be seen to be almost completely destroyed; the mucous membrane is converted into a thick necrotic layer densely packed with polymorphonuclear leukocytes. The submucosa is swollen by edema; the capillary vessels within it may be found to contain numbers of large macrophage cells derived from the endothelium.

Separation of patches of necrotic membrane leaves ulcers which generally lie transversely in the bowel and have irregular serpiginous margins, or in

severe cases extensive raw surfaces. Necrosis does not, as a rule, extend beneath the *muscularis mucosæ*, but it may go deeper, and exceptionally the entire thickness of the gut may become gangrenous.

The acute changes usually involve the entire length of the large intestine, and not uncommonly the last 12 to 24 inches of the ileum.

Chronic dysentery causes numerous serpiginous ulcers in a somewhat thickened and fibrosed mucous membrane, the lesions being usually confined to the lower half or two-thirds of the colon.

In healing the mucous membrane regenerates from the remnants of Lieberkühn's follicles, but when necrosis and exfoliation has been extensive, severe scarring of the bowel is inevitable. Mucous glands may be nipped off in the scar tissue and form cysts.

Bacillus dysenteriæ rarely invades the blood-stream, though occasional cases have been reported.

The changes in other organs are slight and need not be discussed in detail, with the exception of those in the suprarenals. These sometimes show degeneration of, or hemorrhages into, the medulla, which may have a clinical importance in that it causes a loss of vascular tone.

It should be emphasized that the pathological process is essentially a diffuse superficial inflammation of the mucosa, which leads to necrosis, and is in contrast with that of amebic dysentery which starts in the submucosa, and leads to the formation of small discrete ulcers with undermined edges in the mucous membrane with slight or no inflammation of the intervening areas.

Symptoms.—Dysentery has been symptomatically classified into the following groups by Manson-Bahr: (*a*) mild, (*b*) acute, (*c*) toxic or fulminating, (*d*) relapsing, and (*e*) chronic. The fulminating group may be divided into two subgroups—the choleraic and the gangrenous. The symptoms of dysentery vary considerably with the severity of the disease.

Mild dysentery may be merely a diarrhea, although the stools usually contain mucus.

The severity of *acute dysentery* varies greatly. The *incubation period* is about two to seven days. The *onset* is sudden with griping pain in the abdomen, followed shortly by diarrhea. The symptoms increase in severity and frequency, and mucus appears early in the stools. Within twenty-four or forty-eight hours the patient passes typical dysenteric stools consisting of mucus, pus, and blood from five to ten times a day or much more frequently. There is straining or tenesmus on account of the severe rectal irritation. The temperature rises to 101° F. or over. The disease must be regarded as active as long as the temperature is above normal. There may be headache, vomiting, and signs of toxemia, malaise, or drowsiness. The abdomen may be tender over the colon. One patient in the Peking Union Medical College presented at the onset a typical picture of appendicitis.

The *typical stool* in bacillary dysentery consists of mucopus, and varies in color from pale pink to bright red, according to the proportion of blood. Microscopically it is rich in polymorphonuclear leukocytes (90 per cent.) and shows considerable numbers (2 per cent.) of macrophages or large endothelial cells often containing ingested blood-cells and, therefore, liable to be mistaken for *Entamœba histolytica*. Detailed descriptions are given in papers by Wenyon and O'Connor, Duncan Graham, and others. Diagnosis as amebic dysentery of any dysenteric stool containing amebæ is to be avoided, since non-pathogenic amebæ may be found in stools during bacillary dysentery.

Sigmoidoscopy shows a characteristic appearance corresponding to that described above. A swab from the mucous membrane may yield *Bacillus dysenteriæ*, or a scraping, gently taken from the base of an ulcer, may secure amebæ when they have not been recovered from the stools.

The *blood-count* may show a moderate leukocytosis, rarely above 16,000, but frequently the number of white cells is not above normal. The average counts in 90 uncomplicated cases were: Shiga dysentery, 12,338; mannite-fermenting group, 10,063; amebic dysentery, 15,845, average in 14 acute cases (Peking Union Medical College Hospital Series).

Agglutinins appear in the blood-serum usually from the sixth to the tenth day, and, consequently, serodiagnosis is only of value in the later stages of the disease. Dreyer's technic with standard agglutinable cultures should be used with a representative of each type of dysentery bacillus.

The *malignant forms* of dysentery are marked by a very acute onset and severe toxemic symptoms. The *choleraic type*, with vomiting and great loss of fluid, absorption of toxins and collapse, is sometimes mistaken for cholera. The diagnosis is made from the passage of large amounts of mucus, with or without blood, from which the cholera vibrio is absent. The *gangrenous form* also begins suddenly with headache, vomiting, pyrexia, and other symptoms of severe toxemia. The abdominal pain and tenesmus are very great, but later may disappear as the toxemia increases. The stools in the last stages are free from mucus owing to complete necrosis of the mucous membrane.

Mild recurrent dysentery is manifested by a recurrent diarrhea and the passage of a little mucus and blood, which persists when treatment is inadequate in the first attack. The agglutination reaction of the serum usually shows that the infection is due to a Flexner-Y organism.

Chronic Bacillary Dysentery.—Dysentery lasting for over one month is considered chronic. The persistence usually results from inadequate treatment in the acute stage or too early return to a normal diet and activity. The patient constantly passes loose stools containing small amounts of mucus. The condition may last for years and end in death from exhaustion, or may slowly disappear. Proctoscopic examination shows the mucous membrane of the rectum and sigmoid to be red and rough and somewhat edematous, with numerous shallow ulcers; occasionally there may be sessile papillomata or polypi.

Bacillary Dysentery in Infants.—Dysentery is not uncommon in infants, and is a more serious disease in the very young than in adults. It was first demonstrated by Duval and Bassett that the bloody diarrhea of infants was due to *Bacillus dysenteriæ*, and this observation has been amply confirmed by studies made at the Rockefeller Institute under Flexner and Holt and subsequently by many others. The disease occurs in breast-fed as well as in other infants (26 out of 237 cases in Holt's series), may be mild or severe, and causes constitutional symptoms which are not always proportional to the degree of local inflammation as judged by the discharges. According to Davison persistent passage of bloody stools, or of stools containing much pus, is practically always evidence of dysentery infection which can be demonstrated by culture or serum agglutination.

The chief differences between the manifestations during childhood and later life are the greater degree of toxemia in adults and the more striking effects of loss of water. The onset is marked by vomiting and possibly con-

vulsions, and the patient is drowsy, apathetic, and difficult to feed, the temperature may be high, and loss of weight rapid. Death usually occurs in the acute stage, but may result from marasmus after the dysentery has disappeared.

Complications.—*Arthritis* is the commonest complication, and most often affects the knee, although one joint or several may be involved. It is accompanied by fever and a serous effusion into the joint. This is usually sterile, but has occasionally been known to contain Shiga's bacillus. Arthritis occurs after the acute stage of dysentery is over, usually in Shiga infections.

Conjunctivitis and *iridocyclitis* are rare, the latter usually accompanying arthritis. Among other complications may be mentioned *parotitis* due to secondary infection from mouth organisms, *tachycardia*, *endocarditis*, *neuritis*, and *edema* and *ascites* in debilitated patients. An important sequela of severe infections is *stenosis of the colon.*

Diagnosis.—For diagnosis of the disease and observation of the progress of a case a careful examination of the dejecta is essential. It is true that a diagnosis can only be made with positive certainty either by recovering *Bacillus dysenteriæ*, or from a positive agglutination test with the patient's serum. Nevertheless, with experience a correct primary diagnosis can usually be made in acute cases without waiting for bacteriological proof, a matter of critical importance in the early institution of treatment.

The principal diseases from which bacillary dysentery has to be differentiated are amebic dysentery, balantidial dysentery, schistosomiasis, malarial "dysentery," cholera, intussusception, membranous or ulcerative colitis, tuberculous ulceration of the bowel, and carcinoma. Of these, *amebic dysentery* is the most liable to cause an error in diagnosis, but it can be distinguished in most cases by examination of the stools. In a typical case of amebic dysentery the stool is reddish brown and liquid, containing shreds of mucus; the diagnosis is made by finding *Entamœba histolytica* under the microscope. The following points may assist in making a diagnosis:

Bacillary Dysentery.—Onset acute with fever and toxemia; pain and tenesmus severe; stools highly cellular; serum agglutinins present after the tenth day; liver abscess and perforation of bowel so rare as to be negligible.

Amebic Dysentery.—Chronic relapsing colitis; local symptoms less severe; abdominal tenderness localized in certain parts of the large intestine; stools show few leukocytes, macrophages rare, Charcot-Leyden crystals present; liver abscess and intestinal ulceration not uncommon.

Sigmoidoscopy is often of value in deciding upon the diagnosis.

Prognosis.—The mortality varies enormously, and is much influenced by the virulence of the organisms, the character of the treatment, the age of the patient, and the development of complications. During the War it did not exceed 2.7 per cent. in Macedonia, Egypt, and Mesopotamia among the British Forces from 1915 onward. The invalidism caused by the disease is considerable. Although in 50 per cent. of a series of typical cases diarrhea lasted only eight days, the average number of days of treatment for the 2000 cases in the British Army during 1917 and 1918 was 141.

Prophylaxis.—*Carriers.*—In endemic regions food handlers should be routinely examined, and those carrying pathogenic organisms transferred to other employment.

Fly prevention and measures to secure *clean food* are obvious and important.

Vaccines.—Emulsions of the organisms in salt solution produce severe reactions, while oil suspensions are difficult to sterilize. Vaccines treated with immune sera or injected with such sera have been said to react favorably, but are still of doubtful antigenic value. Besredka has immunized rabbits by means of vaccines administered orally. It cannot be said that the value of any of these methods has been demonstrated as sufficient to command general acceptance, but some of them hold out possibilities of success.

Treatment.—General.—Rest in bed is of great importance, and for a patient to return to activity too soon is to court a relapse.

It is commonly advised to empty the bowel by means of $\frac{1}{2}$ ounce (15 c.c.) of castor oil at the outset in order to remove indigestible contents.

The type of *diet* is most important, and must be such as to leave a minimum of residue in the bowel. During the acute stage the fluid intake should be as large as possible, and the nourishment derived only from albumin water, clear tea sweetened with lactose, thin gruels of arrowroot or rice water, jellies, etc.; milk is not suitable at this stage. When the disease is less acute other smooth cereals and citrated milk may be given; and when mucus has disappeared from the stools the diet may be gradually increased by adding lightly poached eggs, crackers and butter, custards, milk puddings, dried toast, fruit juices; and later on by fish, chicken, and mashed potatoes. The return to a normal diet should take place by degrees.

Specific.—The specific treatment of bacillary dysentery aims to neutralize toxins and prevent their absorption.

Sodium sulphate in saturated solution should be given in doses of 4 to 8 c.c. (1–2 drams) every one or two hours day and night when the patient is awake, and continued for twenty-four hours, or until free watery stools are passed. It can then be administered once every four hours. This greatly relieves the pain and tenesmus. Although some physicians are strongly opposed to its use, its action in diminishing absorption justifies the administration of sodium sulphate. The experiments of Macht and Finesilver showed conclusively that a solution of sodium sulphate in an isolated loop of gut prevented the absorption of drugs from that loop; it may be presumed that the salt acts similarly on dysentery toxins. In children, or in adults suffering from dehydration, it must be used with caution or withheld, or given in conjunction with intravenous or subcutaneous injection of saline.

In fulminating cases it is, above all, necessary to forestall collapse by keeping the patient warm and by intravenous injections of normal saline—amounts up to 1000 or 2000 c.c. (40–60 ounces). In the choleraic type Roger's hypertonic saline (sodium chlorid, 8 gm.—120 grains; calcium chlorid, 0.25 gm.—4 grains; water to 568 c.c.—1 pint, 1921 formula) may be given intravenously. In the later stages to prevent constipation a daily morning dose of *magnesium* or *sodium sulphate* is advisable. Rectal injections are not of much value in the acute stage, though a bland fluid such as normal saline may give some relief. Rogers has found that calcium permanganate is antitoxic, and uses a solution of 1 : 1000 (10 grains to 1 pint) for colonic irrigation.

Serum therapy generally gives good results, though not invariably. The polyvalent sera usually employed may be deficient in the antibodies of one

or another of the groups of bacilli. The most striking statistics on the results of serum treatment are those obtained by Willmore and Savage at El Tor, where the dysentery mortality fell from 53 and 63 per cent. in the years 1909 and 1910 to 32.6 and 21 per cent. in 1910 and 1911. The following season, 1911–12, no serum was available, and the death rate rose to 70 per cent., to be again reduced in 1912–13 to 12 per cent. by resumption of the use of serum. Graham states that the mortality was only 1 per cent. in 200 average and severe cases treated with serum. Of a series of 152 cases of bacillary dysentery at the Peking Union Medical College Hospital, 79 were treated with serum; the effect on these was good in 51 per cent., moderate in 25 per cent., and nil in 24 per cent.

The most striking feature of serum treatment is the antitoxic effect in very toxic patients. The average or mild type frequently responds with definite improvement, but as such are likely to improve in any case, the probability of serum sickness and the expense of serum may be weighed in the balance before serum therapy is begun. The earlier in the disease serum is given, the more effective it is likely to be. In acute cases the disease may be immediately cut short when a full dose is given within the first twenty-four hours, but improvement has followed an injection of serum as late as the thirtieth day. Intramuscular injection of large doses is painful; and since the serum is most effective when injected intravenously, it should be administered by this route with proper precautions to insure safety.

Technic.—The patient's sensitiveness to serum should be tested before the *first* dose by an intracutaneous injection of 0.02 c.c. of 10 per cent. serum. A positive reaction appears within one hour, and consists of a wheal surrounded by a red areola. If this is present, the patient must be desensitized by a series of gradually increasing doses given hypodermically at intervals of half an hour, commencing with 0.025 c.c. The quantity is doubled each time until 1 c.c. is given. If there is no reaction, 0.1 c.c. may be given intravenously and followed at half-hour intervals by injection of a dose just double that of each preceding injection. For intravenous injection, serum should be diluted with an equal volume of saline, and given very slowly at body temperature.

Intramuscular injections are best made in the adductors of the thighs. Care must be taken to avoid injury of the femoral artery. The serum may also be given subcutaneously in the flanks or buttocks, but it is more slowly absorbed by this route.

Serum must be given in large doses. It has been the writer's practice to administer two daily injections of from 40 to 80 c.c. each. Some advocate even larger doses (60–120 c.c.). The best results are obtained if the serum therapy is continued until the temperature is normal and the stools are free from mucus; exceptions to this rule are to be made when the serum after three or four days' trial is obviously inert, or in late cases when traces of mucus continue to be passed for a long time.

The use of serum is often followed in about eight days by "serum sickness," manifested by a papular urticaria with fever and possibly arthritis.

The treatment of *chronic dysentery* is a discouraging undertaking, which requires patience and perseverence. *Rectal injections* are the most effective form of medication, and a variety are recommended: calcium permanganate, copper sulphate, tannic acid, eusol, etc. The silver salts probably are the best; albargin (1 : 500) or protargol (0.5 to 1 per cent.) may be tried, but silver nitrate may at times produce the best results. Observation of the effect of such treatment by sigmoidoscopic examination is of the greatest assistance. If the mucous membrane is acutely inflamed as well as ulcerated,

solutions should be diluted to 1 : 1000 or 1 : 500, while for indolent ulceration concentrations up to 1 per cent. may be employed. This stimulates an acute reaction and a reparative process, but should not be repeated too often, as the balance between inflammation and repair is not easy to strike. An injection of 300 to 500 c.c. is usually sufficient, as the ulcers are most often in the lower part of the colon. If the rectum alone is ulcerated, 10 per cent. silver nitrate may be applied directly to the ulcers on a small swab to stimulate healing. The *diet* in chronic cases should be nourishing, and if the patient is very anemic, *blood transfusion* is beneficial.

Surgical treatment may be employed as a last resort. Appendicostomy is of little or no value. As can be seen by *x*-ray examination, the entire colon may readily be filled with a solution given through the rectum. Cecostomy, with the opening of an artificial anus, may, by giving the colon complete rest for three months, prove a rational and sometimes satisfactory mode of treatment, but many if not most patients respond to less heroic measures in a shorter time. *Vaccines* have been tried, but are liable to cause dangerous local reactions. The organisms are suspended in salt solution. Autogenous vaccines, "sensitized" with immune serum, have been recommended.

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TUBERCULOSIS

GENERAL ETIOLOGY AND MORBID ANATOMY

Definition.—Tuberculosis is an infectious process, chronic or acute, set up by a specific micro-organism, the *tubercle bacillus*, and capable of existing without functional disturbance (clinically *quiescent tuberculosis*) or with symptoms and disability (clinically *active tuberculosis*).

Etiology.—The Micro-organism.—The *Bacillus tuberculosis* is a small

aërobic non-motile rod-shaped organism, straight or slightly curved, with rounded ends and sometimes a definitely beaded appearance. It grows very slowly upon culture-media and does not propagate outside the body under ordinary circumstances. The *Bacillus tuberculosis* contains a waxy substance within its protoplasm which is resistant to acids and alcohol after coloration with certain aniline dyes, in this respect resembling the bacillus of leprosy and smegma, grass, and butter bacilli. The organism may be easily demonstrated in sputum and other pathological material by the Ziehl-Neelsen method.

There are three pathogenic types of *tubercle bacilli:* (1) The human, or *typus humanus;* (2) the bovine, or *typus bovinus;* and (3) the avian, or *typus gallinaceus.* Reports of infection with the avian bacillus are so excessively rare that it may be disregarded as a cause of human tuberculosis. The disease in man is practically always the result of infection by the human or bovine bacillus.

Sources of Infection.—The primary source of infection is a tuberculous animal or human being. Tuberculosis occurs so rarely among wild animals as to be of no significance. Among domestic animals it is common only in cattle and swine, as bovine-bacillus infection. Since the bacillus is destroyed by the heat required for cooking, the chances of bovine infection through the food products of hogs are almost *nil.* The same may be said in regard to infection through the eating of beef and veal. The bacilli are, however, eliminated alive and virulent in the milk of cattle with tuberculosis of various pathological forms. *Raw cow's milk* is, therefore, a primary source of bovine-bacillus infection in human beings; indeed, cow's milk and its uncooked products—butter, cheese, etc.—are the only noteworthy animal sources of human infection.

The *dejecta* and *excreta* of tuberculous human beings may, under the proper circumstances of pathological character and location of infection, be primary sources of human infection. These include pus discharged from superficial abscesses and fistulæ, feces, urine, and sputum. *Sputum* far outranks all other human sources combined in importance. It owes this prominence to two major features: first, it originates in and is eliminated from the lungs, which are the seat of immeasurably more ulcerative or, as we say, "open" tuberculosis than any other part of the body; and second, its disposal is not attended with the care and safeguards that are usual with other dejecta. Ulcerative pulmonary tuberculosis of bovine-bacillus origin is excessively rare in human beings. In practically every instance, therefore, infectious sputum contains the human bacillus. *Human sputum is the great primary source of human-bacillus infection; raw cow's milk, of bovine-bacillus infection.*

To all outside destructive agencies except direct sunlight the *tubercle bacillus* is one of the most resistant pathogenic micro-organisms known. It retains viability and virulence after (1) being dried for a year and a half, (2) burial in the ground and exposure to putrefactive agencies for months (according to Schottelius, "several years!"), (3) exposure for several weeks to temperatures alternating, at intervals of several days, from 18° to 27° F. to 37° to 50° F., (4) seven hours at 158° F. and three hours at 212° F. *dry* heat. Protected by the mucoid envelope of sputum *tubercle bacilli* are still more resistant. They are said to succumb to seven hours' continuous exposure to direct sunlight.

This tenacity of life outside of the body makes possible an enormous range and number of intermediate sources of infection. We may assume that for a time, undoubtedly shorter than the periods suggested by the above data, any substance or object contaminated with infectious sputum is capable of setting up infection if the proper human contact is established.

Portals of Entry.—There is no select or exclusive portal of entry *necessary* for infection. To initiate tuberculosis only one condition need be fulfilled for the bacillus; this is, that it be introduced beneath the integument of the body or of its passages to the outside. The bacillus will not evoke pathological reaction as long as it remains strictly on the surface, but once past this and within the body it can begin infection anywhere.

The opportunities and modes of human infection are such that the bacillus usually enters the body by way of the mouth or nose. In nearly every case tuberculosis is received by ingestion or inhalation, or both. In a minimal number of instances the portal of entry is a point on the outside of the body or in the vagina or perhaps the anus or *puncta lacrimalia*. In almost all of these rarer types of infection except that by the lacrimal duct infection is usually associated with trauma. Contaminated surgical instruments may, of course, introduce *tubercle bacilli* into any part of the body and thus originate infection.

Modes of Infection.—*Bovine bacillus* infection occurs through the ingestion of tuberculous cow's milk.

Human-bacillus infection originating from tuberculous *urine* or *feces* is also a consequence of the ingestion, or the hand-to-mouth transference of substances, such as food or eating utensils, that have been contaminated by tuberculous persons. It has its counterpart in what we recognize as a common method of infection in typhoid fever, and is probably responsible for a small proportion of infections.

Human-bacillus infection from *sputum* takes place (1) through immediate contact with a carrier, usually a person with ulcerative tuberculosis of the upper respiratory tract, (2) through direct contact with crude sputum that has been expectorated by a carrier and is dissociated from the latter, and (3) through contact with any intermediate object or substance that has been tainted with sputum. The reception of droplets of mouth spray projected by a coughing consumptive is quite likely the most common example of the first type of contact. Since persons with pulmonary tuberculosis may have particles of sputum on their lips and hands, and transfer them to other parts of the body or their clothes, infection through immediate contact is also a possible consequence of such acts as kissing or the fondling or care of children. Intermediate infection has been ascribed for the most part to the agency of dust, with which expectorated sputum has become incorporated and is then carried to recipients by air currents.

Immediate *infection by droplets* takes place by inhalation, as does also intermediate infection by dust, but it is plain that many who are exposed to atmospheres of dust or droplets will also receive infectious particles by ingestion, that is, through the open mouth or after being deposited on the lips and carried into the mouth by the tongue. Since mucoid raw sputum cannot be wafted about in the air, the mode of its entrance into the body is always by ingestion.

Avenues of Primary Infection.—*Inhaled tubercle bacilli* may settle on

the surface of the mucous membrane of the respiratory tract and be carried through it at any part. The more usual places of their entrance into the tissues are the lungs, the pharynx, and the nasopharynx. From such infections there arise tubercles of the lungs and its lymph-nodes (frequently manifest), of the lymph-nodes of the neck (frequently manifest), and of the tonsils (rarely manifest).

Ingested tubercle bacilli are borne into the tissues of the digestive tract, most commonly in the regions of the mouth, the pharynx, and the lower third of the small intestine. In all probability tubercles of the tonsils and cervical lymph-nodes are set up much more frequently by ingestion than by inhalation infection.

Incidence of Tuberculosis.—The range and extent of tuberculosis in its several phases of infection, illness, and death exhibit relationships that imply the operation of varied etiological forces. With a death rate of approximately 1 per 1000, tuberculosis at present causes about 100,000 deaths a year in the United States (deaths 89,724, rate 91 per 100,000, for registration area, 1922). The number of persons ill with the disease is at any time probably tenfold the number of deaths. Generally accepted estimates, therefore, put the incidence in the United States at about 1,000,000 per year.

Formidable though tuberculosis is as a cause of illness and death, it is many times more prevalent as an infection without illness. Wherever the disease has gained a foothold, the greater part of the population by the age of maturity has undergone infection of more or less permanence. In the more densely populated sections of large cities this "mass infection" or "tuberculization" comes to include almost all the adult inhabitants. From birth, through infancy, childhood, and adolescence it proceeds with great rapidity. Though innumerable children are procreated by parents ill with tuberculosis of every degree, congenital infection is so excessively rare that for practical purposes we may dismiss it as non-existent, but after birth the number of infected persons mounts, very roughly, from 10 per cent. at two years to 20 per cent. at three, 50 per cent. at six, 66 per cent. at nine, and 75 per cent. at fifteen. These entirely approximate figures represent the results of investigations carried on in cities of Europe and the United States. In rural districts and newly settled communities the percentage infected would no doubt be found to be much lower at the earlier ages. On the other hand, there are writers who record an infection incidence in some cities of 85 per cent. at the age of fifteen and over 95 per cent. at the age of twenty-one.

The various pathological and epidemiological studies on the incidence of tuberculous infection throughout the civilized world have arrived at varying percentages of infection for the several decades of life. But without exception all agree on two fundamental propositions: first, that most adults have at some time or other been sufficiently infected with tubercle bacilli to respond with the formation of anatomical tubercle of greater or less permanence; and second, that the vast majority of the infected never become ill with tuberculosis.

These characteristic relations of tuberculosis may be expressed more concretely, and with approximate accuracy, by reference to conditions in New York State. In round numbers the population of the latter is 10,000,000 (actually it is a half-million more). The state is unique in that at pres-

ent there is no great difference between the tuberculosis death rates for the State as a whole, for New York City, for the State exclusive of New York City, and, separately, for the rural and urban districts of the State exclusive of New York City. In every one of the five instances the death rate is a few points above or below 100 per 100,000 population; and this uniformity suggests that throughout this compact geographical division the etiological factors of tuberculosis are fundamentally similar.

Deaths from tuberculosis in the State are, again in round numbers, 10,000 annually (10,695 in 1922), or about 1 per 1000 population, and the number of cases of illness ten times this, or 100,000. Infection tests that have been performed in New York City indicate that in this community the incidence of infection conforms, broadly, with that above set down; and the similarity of death rates for the several demographic divisions of the State warrants the assumption that for the State at large the numerical data of infection would not be radically different—certainly not after the age of adolescence. We may, therefore, believe that at least half the people of New York State (taking into account all ages), or 5,000,000, are infected with tuberculosis.

On this computation the tuberculosis situation is 10,000 deaths, 100,000 cases of illness, and 5,000,000 instances of infection. Therefore, only 1 person out of every 50 infected becomes ill with tuberculosis. There is, indeed, reason to believe that the ratio is even lower, for at any specified time not a few cases of illness represent not new cases, but relapses which are so normally a feature of clinical tuberculosis, just as the inclusion of these relapsed cases in statistics tends to make clinical tuberculosis appear a less fatal disease than it really is; for its ultimate mortality is certainly much greater than the 10 per cent. which 10,000 deaths for 100,000 cases would suggest.

Etiological Deductions from the Data of Incidence.—The implications of the above data are plain and possess considerable etiological significance. The rapidly increasing frequency of infection, which in later life approaches universality, points out unerringly that, under present living conditions, the opportunities for exposure to the tubercle bacillus are boundless and virtually omnipresent. It compels the opinion also that the modes of infection are numerous, and that there must be in operation other major modes than the inhalation of droplets of mouth spray from a consumptive in immediate contact with the recipient; for, frequently as ulcerative pulmonary tuberculosis occurs, it is inconceivable that the majority of mankind undergoes so early in life the exposure necessary for this method of infection. At any rate, the authentic facts of the incidence of infection would compel us to take the most catholic view of the manner in which infection is accomplished; that is, until by scientific demonstration the several possible modes are given their relative place in the scheme of infection, to regard all of them as significant, in proportion as they offer opportunities for contact with living tubercle bacilli.

It becomes apparent also that the factors concerned in the attainment of infection—of infection considered by itself and without reference to its consequences—must be relatively few and simple. By infection is meant the entrance of tubercle bacilli into the body and their continued residence there sufficient to provoke anatomical change and other deep-seated effects, such as allergy to the bacilli or their derivatives. We find this occurring

under conditions that make us believe that primary infection will take place in every person alike. We can detect no races or individuals that are presumably exempt from it, or more or less resistant or immune to primary infection as such. All that we can discover suggests that slight and transient exposure to tubercle bacilli will bring about *infection* in everyone. The exposure is ordinarily so trivial that, if we consider all *infected* people, it is certain that most of them would have no knowledge of any contact having been established; and even in a large proportion of infected (not ill) children, whose comparatively short lives allow us to trace their associations and contacts better, it is impossible to uncover a history of known contiguity with anyone or anything tuberculous.

It follows, therefore, that the only conditions necessary for the accomplishment of infection are the passage of proper portals of entry by *tubercle bacilli* and their entrance into the tissues. Moreover, all discernible circumstances indicate that the number of living and virulent bacilli necessary for infection is very few.

But the fact that out of every 50 or more persons infected only one becomes ill with tuberculosis raises the presumption that if infection is to become capable of producing illness, something more is necessary than the mere presence of *tubercle bacilli* in the body and their capacity to reside there for an indefinite time and arouse the production of tubercles. It points to the probability that the causes of illness from tuberculosis reside in qualities of the bacilli, or of the host, or of both, that are peculiar to the individual case.

It is, indeed, the causes of clinical or active tuberculosis, as distinguished from the causes of infection as such, that constitute the main problem of the etiology of tuberculosis. Put tersely, this problem is: Why do some people get active tuberculosis, while most, though infected, do not? Granting that the factor *sine qua non* of all tuberculosis is the bacillus, practical medicine today recognizes the etiology of tuberculosis as synonymous with the etiology of active tuberculosis, and, as a thing to be explained, regards it as a phenomenon distinct from the etiology of infection as such. The latter is apparently a relatively simple biological event; but its subsequent course is beset with many complexities which mold and determine its issue.

A. Properties of Infectious Agent as Etiological Factors.—Type, virulence, and so-called "dosage" of *tubercle bacilli* each play a part in shaping the course of every infection.

1. *Type of Tubercle Bacillus.—Pulmonary tuberculosis* is responsible for from four-fifths to nine-tenths of all deaths from tuberculosis. The ulcerative or clinically active types are caused by the *bovine tubercle bacillus* with such rarity (for instance, in 5 of 811 cases collected by Kossel) that in practice we are accustomed to regard them as exclusively of human-bacillus origin. There can be no doubt that *bovine-bacillus infection* of the lung occurs, and that it not infrequently accompanies or is the metastatic consequence of bovine-bacillus involvement of lymph-nodes, bones, joints, etc. Why it does not develop more often or progress to clinically manifest proportions in the human lung is obscure. It is, however, significant that experimental infection of cattle with human *tubercle bacilli* also results in symptomatic and disabling involvement of extrapulmonary structures and non-progressive infection of the lungs.

In the absence of more exact information we view the non-occurrence of bovine disease of the lungs in terms of *virulence;* that is, bovine bacilli are less virulent for mankind than are human bacilli. The idea may be correct, but it must be remembered that it is derived not from direct evidence, but from the comparatively low mortality due to bovine-bacillus infection, which is again the result of minimal pulmonary disease set up by it. There is no proof that bovine bacilli exhibit *essentially* less virulence than human bacilli in causing tuberculosis of lymph-nodes and of bones and joints. At the same time they may bring about fatal infection through meningitis and generalized miliary tuberculosis (in 10 per cent. of 33 cases of the former, and 25 per cent. of 178 cases of the latter, according to Kossel).

In general, we may regard the type of *tubercle bacillus* concerned in any infection as contributing to the end-result. Infections by bovine bacilli are likely to be relatively benign because they do not give rise to active pulmonary tuberculosis. They are, however, potentially malignant because they may precipitate meningitis or generalized tuberculosis.

2. *Virulence of Tubercle Bacillus.*—Broad differences of virulence pertaining to *type* of bacillus have been mentioned in the foregoing paragraphs.

In seeking to explain the remarkable multiplicity and diversity of effects of tuberculous infection, and in the absence of direct observation, nothing is more natural than to ascribe these almost innumerable differences to variations in virulence of the bacillus. The idea, usually a gratuitous assumption, has had but slight support from more exact studies. Investigators are practically unanimous in reporting that the net results of inoculating susceptible animals with tubercle bacilli derived from the greatest variety of tuberculous processes, indicate a remarkable uniformity of virulence for the many different strains of the same type, in so far as this can be determined by the character and invasiveness of the infections in the inoculated animals. Moreover, even when occasional differences of experimental infection have appeared, it has been impossible to correlate these with the character of the lesions that were the sources of the bacilli.

At present, therefore, we are not inclined to regard virulence as a decisive variable in the general run of tuberculous infections. It is much more in accord with ascertained fact to look upon all living bacilli of the same type, and derived from active foci of a patient, as possessing approximately the same powers to "take hold" in the body and arouse pathological reaction.

3. *So-called "Dosage" of Tubercle Bacilli.*—Whatever may be the actual effect of type and virulence of bacilli concerned, all observers agree on the importance of *"dosage"* in determining the character of infection.

By "dosage" we mean the number of living bacilli that enter into the act of infection. Strictly speaking, this definition takes account only of quantity, but in considering "dosage" we may also view it in terms of number and time, that is, of the repetition, or frequency of repetition, of reception of *tubercle bacilli,* and of the length of the intervals between contacts with the bacilli.

Experiment shows with great regularity and definiteness that after single inoculations the gravity of the infection corresponds, within broad limits, to the number of bacilli introduced. If this be large, the first evidences of tubercles appear rapidly, and infection pursues a fulminant course; if small, the early manifestations are delayed, and infection evolves with all

the familiar earmarks of chronicity; if minimal, there may even be a prolonged period of latency or quiescence, or, on occasion, a condition of practically permanent quiescence, although anatomically all infection is not obliterated.

The effects of repeated infections are variable, with differences dependent largely on the numbers of bacilli entering into the several separate infections and on the intervals of time between them. A single primary infection raises the resistance to later infections. This specific immunity is never in any instance complete; that is, it gives way before excessively heavy reinfections, with results that may be *immediately* more disastrous than if the severe infection had been a first infection and had been received by a normal individual with native susceptibility.

After a primary infection has been received it takes from ten days to three weeks or more before a measurably competent immunity is established. It is, accordingly, obvious that if each of two animals or persons underwent a dozen infections that were identical in quantity and virulence, the results would be entirely different if in one the separate infections took place daily, and during that period in which immunity had not got under way, while in the other they took place at intervals of a week or more. In the first instance there would result a summation of infections, unopposed and unmitigated by an increased resistance; in the second, all infections except the first, unless too large, might be disposed of with slight effect.

In actual life the opportunities for infection, as regards numbers of bacilli, frequency of contact with them, and intervals between contacts, vary enormously. There are numerous persons of every age so situated that exposure to tubercle bacilli is minimal, transient, and only very occasional or unrepeated. There are many others, for instance, the members of a careless consumptive's household in the slums, who for months may dwell in an environment of unremitting exposure and who take in large numbers of tubercle bacilli many times daily. We shall see that the factors that influence the evolution of tuberculous infection are so diverse that it is frequently difficult in a given case to determine with certainty the particular agency responsible for the outbreak of active tuberculosis. It is, moreover, always impossible to ascertain all the several contributory factors, and to give each its relative weight in the production of the end-result, but it is certain that in every instance in which they have been operative, heavy or, as we say, "massive" infection, frequently repeated infection, and very short intervals between repeated infections have had a share in favoring the establishment of progressive rather than limited tuberculosis

In this connection one may also mention the great importance of the intervals between separate reinfections in those who are already relatively immune through previous infection. Tuberculosis is no exception among infections to the general immunological law that for a short time (twenty-four hours more or less) after single reinfections the immune animal experiences a fleeting condition of diminished resistance—the period of so-called *negative phase*, etc. Those, therefore, who are in grossly contaminated surroundings run the risk of being reinfected at such brief intervals that some infection may occur within this period of lowered resistance, and, if large enough, hurry a really immune person into active and progressive tuberculosis.

Taken all in all, we are inclined to consider the contingency of *frequent*

repetition and *brevity of interval* between repeated infections as more likely to condition the activity of infection in more persons than is quantity or "massiveness" of the single infections; that is, if we take into account conditions of life and social relations, as they actually are, and the opportunities for infection that these engender.

B. Properties of the Host or Recipient of Infection as Etiological Factors.—Tuberculosis is almost unique among infections, in that it has, properly speaking, no period of incubation. Infection of the body is accomplished, and the anatomic marks of infection come into being and may remain indefinitely long (for months, years, or a natural lifetime) and the body meanwhile never exhibit symptoms of disease. On the other hand, it is certain that, when active tuberculosis does make its appearance, in the vast majority of instances it is the expression of an infection that originated a comparatively long time previously (weeks, months, or even years before), and during all this time has resided in the body in a state of clinical quiescence, that is, without noticeable effect on the bodily economy. In the susceptible animal we can, with sufficiently large quantities of virulent bacilli, induce a type of infection that progresses uninterruptedly from the first appearance of tubercle a week after infection to death a few weeks later. There have been human cases in which the conditions and course of infection have been essentially similar to those in guinea-pig experiments. Such are the gross infections of newborn infants during the operation of ritual circumcision, when the bacilli (in sputum) have been introduced into a wound and the infection has consisted in placing large quantities of bacilli in a single depot beneath the skin—thoroughly unnatural conditions of infection for human beings. But under the usual conditions of natural human infection an uninterrupted evolution hardly ever takes place. The interval between infection and first appearance of symptoms is indefinite and irregular even in most infants and children.

These features of tuberculosis make it plain that factors which concern the infected individual are largely responsible for the course which particular infections take. That is to say, there are variables peculiar to the soil which, through their interaction with variables of the seed, determine quiescence and activity of infection. Just as properties of type, virulence, dosage, and frequency of intake of bacilli play their part in making activity or progressiveness more or less likely, so do fixed or transitory features of the animal economy contribute to the outcome of infection.

Every modifying agent must, of course, be either constitutional, that is, it must exert an influence on infection through forces that proceed from some abnormality of bodily function; or it must be more limited or local, that is, it must operate through disturbed function of the tuberculous part alone. In the first instance there is good reason to believe that the constitutional factor brings about local effects which are merely a part of a general process; for instance, *fever*, a constitutional phenomenon, may affect respiration and circulation, which, when thus rendered abnormal, might react unfavorably on pulmonary tuberculosis. On the other hand, a strictly local force, such as *trauma*, if applied to a tuberculous part, may activate the infection locally without causing (otherwise) any constitutional disturbance whatever.

Strictly speaking, there are only two general classes of factors relating to the recipient of infection which can have an etiological bearing on infection. Such factors must comprise either (1) inborn peculiarities, features

and tendencies that are of particular significance in relation to tuberculosis or (2) any and all postnatal experiences that may influence the reception of infection or its evolution after reception. We are accustomed, therefore, to speak of (1) *inherited factors*, inborn determinants, and (2) *environmental factors*, determinants derived from experience. Both of these types set in play forces that promote or impede the evolution of tubercles.

1. *Inherited factors* would apply to individuals, to families, and to races. It has already been pointed out that infection tests indicate that all individuals, without regard to nativity, are susceptible to tuberculous infection. Every person is apparently infected when brought in contact with living, virulent *tubercle bacilli* for the first time. There is no evidence whatever that people differ in their native ability to escape infection.

But there is strong presumptive evidence that individual, family, and racial differences of resistance come into play after infection is established, and then modify the latter's course. Tuberculosis, as a cause of illness and death, is notoriously a *family disease*. Nothing about it has been known longer than that it recurs in many families, generation after generation, with abnormal frequency and severity. There can be no doubt that the mortality from tuberculosis is far higher among victims with a family history of the disease than among those whose families have had little or no tuberculosis. The tuberculosis death rates are much higher, and the clinical types of disease allegedly more malignant for *primitive races and peoples* among whom tuberculosis has been recently introduced than for those of older and "long-tuberculized" civilizations. In the latter, moreover, *the negroes*, now partakers of the white man's civilization for several centuries, suffer double and treble the mortality of the whites. The several race and family stocks of the whites seem to withstand the disease with varying success, for its death rate is relatively low for the Jews and relatively high for the Irish.

Whenever clinicians and epidemiologists have used these facts to support an opinion that factors transmitted by heredity modify tuberculosis etiologically, they have been met by equal authority that would attribute such individual, family, and racial differences to circumstances that were not inherited, to diversity of habits, customs and modes of living, to variable opportunities for infection, to different general economic and hygienic conditions, and to their environmental agents. Meanwhile, some statisticians (Pope, Pearson, Göring, Drolet, Pearl) have sought to examine the part played by heredity in a more scientific manner, and after making the proper corrections for environmental influences. Trained statisticians have, for the most part, in this way made out a positive case for heredity; but, again, there has been considerable criticism, not so much of their methods of approach, as of the validity of the data with which they worked.

Whether or not there are *inherited characteristics* that make for or against tuberculosis can quite likely be decided definitely only by experiment. While there are reports of such experiments, practically all of them are trivial and of no consequence. The only studies of this nature that are at all significant are the comprehensive investigations that have been under way for several years by Lewis. He has found that there are definite differences of resistance to tuberculosis among individuals of the same animal species, such as rats, guinea-pigs, and rabbits. There were marked differences among inbred families of guinea-pigs, and a high resistance in one of

the families was transmissible "by each sex to the offspring of each sex in crosses with other inbred families." This is undoubtedly the most exact information that we have yet had on the existence of an inheritable factor of resistance to tuberculosis.

2. *Environmental Factors.*—As has been mentioned above, environmental factors comprise all postnatal personal experiences that can be shown to have an influence on the manner in which the body receives *tubercle bacilli* and on the course of whatever tubercles may be established. From this point of view a specific immunity acquired after birth is an environmental factor (or the result of one), as is the acquirement of any non-tuberculous disease that may affect the body's capacity to resist the implantation or the subsequent development of infection. If pregnancy and its natural sequelæ, otherwise normal physiological incidents, exert an effect on tubercles in particular instances, they are environmental factors. In the same sense, trauma, occupation, diet, the physiological disturbance or dys-equilibrium of puberty and the menopause, personal excesses of work, play, vice, or emotion, may become environmental factors. The economic condition of a person, family, or class is an environmental factor of the broadest and most inclusive kind, for it determines the physical (as well as psychic and social) *milieu* of each—the housing, diet, clothing, recreation, sanitary and hygienic necessities and conveniences, medical facilities, etc., which are fundamental in setting the standard of general health.

There is no other infection that reacts so definitely and yet so delicately to outside or environmental influences. It can be stated almost as an axiom that both the morbidity and mortality curves of tuberculosis for a community will run parallel with the curves for disease and death in general; which means that where the general standards of public health and hygiene are low there is much tuberculosis and many deaths from it, and *vice versa*. Exceptions to this rule arise only with the occurrence of some unexpected public calamity, such as famine or pestilence, by reason of which the ordinary economic and hygienic conditions of a community are suddenly set at naught.

It is also a universal phenomenon that in any given community the tuberculosis cases and deaths increase among the several classes as financial resources become less, and decrease as these grow more ample. In other words, the incidence of tuberculosis rises as people are deprived of comforts and as the struggle for a livelihood becomes harder. It must be remembered, however, that this very circumstance gives rise to an unfavorable physical environment, to the crowded, dark, and dirty living conditions that multiply opportunities for infection.

In clinical practice the influence of environmental factors on tuberculosis in the individual is plain and definite. It is an almost daily experience to find the first symptoms of disease develop after more or less complete recovery from other infections, such as measles, influenza, tonsillitis, pneumonia, bronchitis, or the several varieties of the "common cold." In not a few instances the outbreak of tuberculosis during the course of *diabetes mellitus* is certainly more than casual and coincidental. *Pregnancy, parturition, the puerperium,* and *lactation* frequently usher in a first attack of tuberculosis, just as they many times re-awaken to activity a tuberculosis that had been arrested or clinically "cured."

A sudden *hemoptysis,* followed by illness from tuberculosis, may be

brought on by unusual physical effort, such as a foot-race; or it may come on almost immediately after trauma to the chest. *Pneumothorax* has occurred under the same circumstances, when physical examination revealed the existence of long-standing though previously inactive pulmonary tuberculosis. A slow or acute development of active tuberculosis is a common result of prolonged or more *concentrated physical or mental strain.* Insufficient feeding, leading to a state of malnutrition, is a contributory etiological factor that has gained enormously in significance since the Great War, during which many observers drew attention to the fact that the incidence of tuberculosis increased far more in countries with greatly reduced food supplies (Germany, Austria, Serbia) than in France, Belgium, and England, which suffered less deprivation.

One might go on and specify almost without end concrete environmental factors that influence tuberculosis. In brief and in general, we regard as a potential etiological force in tuberculosis any and every environmental influence that has in it the capacity to activate infection already present. And an activating agent accomplishes this effect, for the most part, through putting the body, or an involved part of it, under physiological strain, and thus disturbing those relations between the body and tubercle, and between the infected part and its contained tubercle, that had formerly held the infection in abeyance.

Active tuberculosis is a disease of *every age,* with its death rate highest in the fifth decade among city-dwelling males and lowest in the second half of the first decade. But it is probable that more *first* outbreaks of the disease occur in the third and fourth decades of life than at any other period; that is, *the breakdown from active tuberculosis is most likely to come not at an age of diminished vigor, but at the time of greatest stress of environment.* For several decades there has been so steady and marked a decline in the tuberculosis death rate as to make the phenomenon perhaps the most outstanding and sensational feature in public health. All ages and races and *both sexes* have participated in this fall of the death rate. The only noteworthy exception has been the circumstance that latterly, since women have entered industry, the tuberculosis morbidity and mortality have tended to increase among women of wage-earning age. Tuberculosis has, in general, been much more prevalent among men than among women; and the fact has been attributed to the more protected and less strenuous lives of the latter—in other words, to their more favorable environment. A chart recently published by Drolet illustrates strikingly the effect of environment on tuberculosis. The chart depicts the tuberculosis death rate, according to sex and age, for New York City for 1910 to 1920. During the first four years of life the rate for males is slightly higher than for females. At the beginning of adolescence that for females goes ahead of the rate for males, to fall below the latter after puberty is established and remain well below it during all the rest of life. While the female death rate continues much lower than the male rate, it reaches its peak a full decade earlier than the latter. It is highest during the period of full reproductive power and most trying home cares, after which it gradually subsides.

All the evidence that we possess indicates unerringly that environment is the most potent force in shaping the course of tuberculous infection, just as it is all important in presenting opportunities for the reception of infection. Notwithstanding the difficulty of obtaining exact information on the part

played by native constitution, or inherited factors in etiology, we must assume also that these exist and exert a real influence. Yet another fact which is only too often forgotten is plain. This is, that whatever may be their quality and capacity in resisting tuberculosis, inherited factors are always modifiable—for better or for worse—by environment. And it is the latter, therefore, which is the really decisive force in the etiology of tuberculosis.

The Etiological Significance of Acquired Immunity to Tuberculosis.—It has been repeatedly stated that a vast proportion of tuberculous infections remain inactive or clinically quiescent. Many of these inactive processes endure for years and perhaps a lifetime. Many heal completely and leave a scar. Many no doubt heal, resolve, and disappear.

It has also been mentioned that the non-tuberculous individual possesses no specific immunity to tuberculous infection, for the rapid and almost universal tuberculization of all sorts and conditions of men, provided opportunities for contact with *tubercle bacilli* exist, allows no other opinion.

As soon, however, as these numerous primary infections are accomplished the recipients become endowed with an increased resistance to reinfection; that is, tuberculous infection renders the body immune to new contacts with outside bacilli and, no doubt, immune as well to the further progress of the primary infection that has taken place within the body.

But the immunity is never at any time absolute; nor, because it has come into being, is it permanent. In no case can it withstand reinfection with unlimited numbers of bacilli or frequent reinfections repeated at short intervals. And in its operation it acts more *to modify the effects of reinfection than to prevent the added bacilli from exerting any effect whatever.* It sets up a reaction between body and bacilli that tends eventually to chronic and limited tuberculous formations rather than to the more progressive and disseminated foci that the reinfecting bacilli would otherwise bring about if they were causing first infections. Moreover, in every case its capacity or competency varies from time to time with the forward or backward movement of the infection that has given rise to it. As infection advances, immunity grows stronger (there are certain reservations to this rule); as infection retreats, immunity becomes less; and, as it heals and is obliterated, immunity disappears entirely and the body again possesses only its native resistance (or susceptibility) to infection.

At the same time immunity in the presence of infection is modifiable by personal experience and environment. It is probably always affected by an acute, non-tuberculous, febrile disease when it is for the time being diminished. The more acute and the highly febrile phases of tuberculosis itself may blunt it greatly. Pregnancy and its sequelæ often seem to influence it markedly; and there is good reason to believe that conditions of functional depression due to such causes as fatigue, malnutrition, etc., depress specific immunity to tuberculosis.

It is plain that, as tuberculosis becomes endemically far flung throughout a community, the etiological influence of its conferred immunity will be profound. Though numerically the opportunities for first infection come to be boundless, the single first infections obtaining in a civilization that has progressed to a relatively high hygienic level (such as ours) are, for the most part, comparatively mild—too slight to proceed at once to active

disease, yet sufficient to set up, for a time, a competent immunity against the greater and repeated infections that may be suffered later. But the main effect of this general state of increased resistance will most likely be manifested in a high proportion of cases of chronic tuberculosis in the total number that becomes active. That is to say, if a large part of the population lives in a condition of relative immunity because of the existence of inactive tubercles, it will respond to sufficiently great reinfections with chronic active tuberculosis, or when the tubercle already present is made active by the proper environmental force this will also tend to assume a chronic rather than a fulminant character. In other words, as a community or a civilization becomes more and more thoroughly tuberculized, whatever infection responds to the stress of environment with activity will tend more and more to be relatively chronic and benign.

The frequently expressed opinion that most or practically all active tuberculosis of adults (usually pulmonary) develops out of infection laid down in childhood, carrying with it the correlative idea that adults are practically immune to reinfection from without, has not been scientifically proved. Indeed, there is just as good evidence to indicate that much adult pulmonary tuberculosis occurs in its typical location and takes on its characteristic chronic course because it represents recent reinfection of soil made immune by previous inactive infection. Opie has done much to lend support to this view through pathological observations, and the experimental biologist and student of immunity, who are accustomed to observe the working and qualifying features of tuberculosis immunity, will also lean toward a similar idea. Nevertheless, clinical medicine presents numerous cases that leave no doubt that a respectable proportion of first attacks of active tuberculosis in adults are the belated fruition of infection that was laid down decades earlier in life. On available information the only reasonable opinion to entertain at present is that, while much childhood infection persists latently and develops later into active adult tuberculosis, much adult tuberculosis is also the consequence of adult reinfection from without.

General Morbid Anatomy of Tuberculosis.—The characteristic anatomical change set up in tissues by the activities of tubercle bacilli is a new formation of nodular or spheroidal nature. Within this pathological structure are enclosed the bacilli. After the focalization of bacilli at any point the change appears in from one to several weeks; that is, comparatively early if bacilli at one spot are numerous, late if they are few. This firm, minute nodule is elevated above the surface, is paler than normal tissue, and evidently bloodless; at first the surrounding tissue also gives few signs that suggest inflammation.

Such nodules increase their size with variable rapidity. They also assume the greatest diversity of size as they tend to maintain a roughly spheroidal form. In some instances they never grow larger than the smallest specks just within the range of vision; in others they come in time to occupy the greater part of an organ. They are commonly as large as a pea, a cherry, or a walnut. It is these structures that have given to the disease its fundamental nomenclature; for from *tuberculum*, meaning *small nodule*, have been derived the names of the pathological changes, the disease, and the micro-organism.

Tubercles increase their boundaries by concentric growth of individual nodular processes or by the gradual approach and ultimate fusion of several

separate processes that have originated near one another. An individual tubercle enlarges as the bacilli within it continue to live and multiply, and are carried from the center to the periphery of the mass; here they stimulate the formation of a new tubercle, which is then added to the structure already in existence. Separate tubercles develop close to one another when an avenue of dissemination carries bacilli into the same neighborhood and deposits them at adjacent points, or when bacilli are conveyed from the interior of a tubercle to points nearby. In the first event the foci may be of the same age or of different ages; in the second they are, of course, of different ages.

Soon after a tuberculous mass is formed it becomes the seat of two contrasted pathological processes. These are *necrosis*, or the degeneration and death of tissue; and *fibrosis*, or repair. Necrosis always begins at the center of the mass and tends to spread outward; fibrosis first involves the periphery and proceeds inward. If *tubercle bacilli* continue to live and multiply within the mass, the central necrotic portion tends to enlarge and encroach upon the fibrous shell that has been built up around it. If bacilli die out, or if they are few and relatively inactive, the fibrous envelope, growing wider and denser and extending inward, replaces the central necrotic tissue, and thus gradually converts the entire mass into a scar.

Therefore, a primary tuberculous lesion consists fundamentally of a newly formed tissue which, if its evolution continues, undergoes necrosis from its center outward and fibrosis from its periphery inward. This new tissue is formed largely by *proliferation* of the cells which react to peculiar chemical constitutents in which tubercle bacilli are very rich. From 30 to 40 per cent. of the bacterial substance consists of lipins; and from 60 to 70 per cent. of these lipins is a waxy substance alleged to be a lauric acid ester of a higher alcohol. When introduced into the body in sufficient quantities *dead tubercle bacilli* also stimulate the formation of typical tubercles. The extracted and isolated wax of the bacilli likewise causes the development of essentially similar structures. These phenomena suggest that, fundamentally, tubercles result from the proliferation of cells reacting in this manner to a foreign body of high stability—the waxy substance of the bacilli. If this conception is correct a tubercle is a structure which serves, with more or less competency, to invest the micro-organisms and wall them off from the rest of the body.

The necrosis of a tubercle is also rather characteristic. Physically, the tissue of these foci resembles nothing so much as certain kinds of firm cheese, and *caseation* has long been a descriptive term applied almost specifically to the necrosis of tubercles. As caseation progresses the involved tissue becomes more and more friable, and at this stage in a pigmented organ like the anthracotic lung, with its greenish and blackish mottling, caseous areas may look strikingly like Roquefort cheese. There is frequently a disintegration of necrotic tissue while it is comparatively dry, when it appears crumbled and ragged in cut section; but in normal necrosis the tissue softens and liquefies, and is thus converted into pus.

If a tubercle is near a surface such as the skin, the mucosa of a visceral duct, or the serous lining of a body cavity, and the necrotizing process extends outward until it reaches the surface, the superficial tissue is involved and may break down. Thus an ulcer forms, the caseous interior of the tuberculous process comes into direct communication with the outside, and,

as it turns to semifluid or fluid pus, is evacuated through the ulcer. As tissue is destroyed and cast out a cavity is formed.

While the interior of a tubercle is undergoing death and destruction of tissue, some fibrosis is always going on at the periphery. If the tubercle is developing with exceptional and excessive rapidity, the marginal portion may be represented by an extremely thin, filmy, and delicate envelope of loose fibrous tissue, and be recognizable only with the microscope; but ordinarily the development of a tubercle is a gradual process, permitting fibrosis which is readily and plainly visible. Every tuberculous lesion that has not healed completely—that is, that has not been entirely transformed into scar tissue—becomes encapsulated, therefore, almost from the very beginning. This is of the greatest significance in comprehending the physiological relations of tubercles and the infected body, from which, of course, the clinical evidences of the infection proceed.

For, as we have seen, at the very beginning cells, which are aroused to activity by bacteria of hardy constitution, proliferate to form a mass that engulfs these waxy parasites and shuts them in. The next step is the deposition of fibrous tissue in the outer layers of this mass. If, at this stage, interned bacilli survive and multiply, and begin and continue activity that kills and destroys tissue, the fibrous envelope, already increasing in diameter and strength, acts as an obstacle to the passage of harmful necrotic products as well as of *tubercle bacilli* into the body, while at the same time it impedes the ingress into the mass of bodily substances of nutritive value to the bacilli. In active tuberculosis the extent of anatomical change plays, of course, a rôle in determining the degree of activity and the severity of the disease. Nevertheless, with everything else equal, it is the *character* rather than the *extent* of the pathological process that counts most; for relatively abundant and increasing fibrosis usually means low-grade and diminishing activity, while slight and relatively lessening fibrosis is reflected in growing intensity of symptoms.

The fibrous envelope may be intact, but if not completely competent it allows the escape of degeneration products which poison the body, or of bacilli which establish new foci in other places. This, of course, is a very frequent occurrence, and happens to some extent in every case of active tuberculosis. Interned bacilli may also be carried into the capsule and there form a fresh tubercle, which caseates. Thus, through a succession of fresh, caseating tubercles the fibrous envelope of a larger tubercle becomes itself invaded by the caseating process, which, if unchecked, causes ulceration. At the same time the entire tubercle increases in size as new fibrous investments form around the tubercles that have developed at or near the periphery of the older mass.

On the other hand, as has been mentioned above, the more central necrotizing process may cease with the death or loss of vigor of bacilli, and the necrotic tissue may be gradually replaced by scar tissue; or lime salts may be deposited in the necrotic tissue in amounts sufficient to form stony concretions—the well-known lung stones, or *pneumoliths*—which are contained within dense and relatively thick fibrous rings; or after evacuation of material the resulting cavity may become thoroughly cleansed of caseous and purulent material, and become in time sterile; and the fibrous tissue, through contraction and shrinkage, may then greatly reduce its size and, if the dead space is not too large, perhaps completely obliterate the cavity.

But *tubercle bacilli* are capable of setting up pathological changes that are entirely different from those of a proliferative nature that initiated the changes outlined above. They also arouse reactions that are essentially and predominantly *inflammatory;* that is, reactions that are characterized by exudation of both the fluid and cellular elements of the blood rather than by proliferation of existing cells.

If the development of superficial tubercles which are accessible to observation is watched, it may be seen that after *primary* inoculation nodular structures arise out of a pale and non-inflamed base. By the end of two or three weeks after inoculation, that is, a few days after the nodule appears, a zone of varying width of what is manifestly inflammation is seen to surround the tubercle. Indeed, soon after the primary tubercle is formed by proliferation, it usually itself acquires some characteristics of exudation. Microscopically, leukocytes are seen distributed through the proliferated mass: first, at the periphery, where they are always most numerous, and afterward in greater or less profusion throughout. As nodular tubercles continue to grow they are prone to acquire more and more marked inflammatory features. Leukocytes, mainly of the lymphocytic order, increase within them, and, although tubercles are avascular themselves, from their periphery and into the surrounding tissue there extends for a variable distance an area of inflamed tissue. It is plain that the nodular tubercle irritates the surrounding tissue.

This is seen most clearly when the tubercle has already been in existence some time and eruptions of tuberculous material into new locations take place from it. Then, where the material lodges, there develops almost immediately an inflammation, the severity and extent of which vary directly with the numbers of newly focalizing bacilli. If an animal is already tuberculous, an inflammation that may go on to necrosis and sloughing appears in the skin a few hours after bacilli are reinoculated there; or areas of pneumonia develop in the lung if the reinoculation be intravenous; or pleural effusion takes place on intrathoracic reinoculation.

It is a fact of prime importance in our entire conception of the pathological changes of tuberculosis that such inflammations never take place after the *first* introduction of tubercle bacilli. Then the first noticeable (macroscopical) effect is the more indolent development of a nodule—the result of proliferation. On the other hand, the tissues of a body that is already tuberculous react promptly with exudation to metastasis from within or to reinfection from without, and at the same time retain their native capacity to proliferate and form a nodular tubercle.

Therefore, after a body has become tuberculous, the pathological changes set up by the infection become highly complicated; for as soon as a tubercle is established these changes may be inflammatory or proliferative, or every combination of these two processes. It can now be understood why primary nodular tubercles show a surrounding zone of pink or red about two weeks after inoculation, for at this time is established a tissue *hypersensitiveness,* or *allergy,* that has been caused by the primary infection; and the allergic state is expressed by an inflammatory reaction to living or dead *tubercle bacilli* or to their dissociated products. It is even possible that the necrosis and the caseation, which involve a tubercle in that part where the bacilli are present—where they are living and multiplying, and dying and disintegrating—is a manifestation of allergy. It is not the effect of any

known essential toxin of the bacilli, and does not result, as some have thought, from the ischemia of an avascular process, for the common central necrosis of the minutest miliary tubercles in normal tissue goes far to disprove such an idea. It is more probably analogous to or identical with the necrosis which a sufficient amount of dissociated tuberculoprotein (tuberculin) brings about in the skin (or other tissues) of a tuberculous animal, although it has no effect on the skin or tissues of a normal animal. In both instances the necrosis is the result of tissue allergy.

Tuberculosis is eminently a metastasizing infection, characterized, if it progresses, by successive eruptions of new foci in many parts of the body. We have seen that in natural human infection tubercle bacilli almost always enter through the mouth and nose; and that, settling upon the mucous membranes of the respiratory and digestive tracts, they may be carried into the submucous tissues, where they can initiate tubercles. Habitually, therefore, infection begins in the domain of the lymphatic system, and any further extension of it is at first centripetal, by lymphatic vessels, toward the center of the body; and, if the passage of bacilli along lymphatics is not interrupted by the numerously intercalated lymph-nodes, the destination of bacilli is the venous system, which conveys them to the lungs. Here, again, a system of continually narrowing blood-vessels favors at least temporary fixation of the bacilli in the vessels and capillaries of the pulmonary tree, while all bacilli that are not thus trapped continue and are distributed by the systemic arteries to the rest of the body.

It is an excessively rare event, if it ever occurs, to have tubercles originate within the lumen of a blood-vessel through the proliferation of the intima. Even though bacilli enter the blood-vessels directly, vascular tubercles are found to begin in the lymphatics of the adventitia and from there proceed to involve the vessels; in other words, embolized bacilli are carried from the lumina of vessels in which they lodge out into the lymphatics. The blood-vessels are important carriers and distributors of *tubercle bacilli*, but anatomical tubercles develop in and extend by lymphatics or in interstitial tissue. Accordingly, whatever bacilli reach the lungs in the blood, and are there caught in the finer vessels, are again carried out of these into the pulmonary lymphatics, in which (or in the numerous collections of intrapulmonary lymphoid tissue) they may set up tubercles at any point within the lung or be conveyed to the lymph-nodes at the hilum. Similarly, inhaled bacilli that reach the submucosa or subepithelial tissue of the lung begin their intrapulmonary career intralymphatically.

Bacilli of primary infections establish tubercles (not necessarily evident) in the submucous tissue close to their point of penetration, but some of them are mobilized with extreme facility and rapidity by the lymphatics which within a few hours carry them to adjacent lymph-nodes. If these nodes fail to intercept all such bacilli in movement, those that pass through follow the paths mentioned above. Thus, *within a few days after infection*, and before anatomical tubercles have come to view, nests of bacilli—potential foci of tubercles—may be scattered in many places throughout the body. Experiments show this unerringly. But it must not be imagined that, necessarily, visible tubercles develop at once or ultimately at all these places. They are formed where enough bacilli have lodged at one point or where intercurrent etiological factors may favor their survival and later multiplication. It is obvious that as we proceed inward, from the point of

penetration toward the center of the body, the numbers of bacilli at successive foci decrease; and their distribution and quantity at any point depends on the numbers that first enter the body.

Accordingly, tubercles of primary infection are most likely to appear *early* at or near the point of penetration, next in the related lymph-nodes, and so on; yet the tubercle that ultimately attains the greatest prominence need not be the first formed. For instance, lesions of the lymph-nodes may far outstrip those near the surface, from which the bacilli came to the nodes; indeed, they may be advanced and active, though the original focus has healed and can hardly be found. In the same way manifest and advanced lesions of bones and joints, kidney, etc., may be active, although the focus that sent bacilli to these places has never caused symptoms and may be pathologically insignificant.

After an anatomical tubercle is established in the body conditions change and become more complicated. The acquired allergic state endows the tissues with the power to react promptly with inflammation whenever and wherever bacilli of metastasis or of outside reinfection lodge. This rapid reaction tends to fix bacilli almost at once, and thus bar that facile migration which is permitted before allergy develops and when the only reaction which the body can display is the rather leisurely development of nodular tubercles.

Metastasis occurs when tubercles ulcerate and discharge their contents into adjacent channels which disseminate infection. There are three main pathways of this nature: lymphatics, blood-vessels, and visceral passages. Smaller lymphatics carry bacilli to lymph-nodes; main lymphatic trunks, to the veins, and thus to the lungs and beyond. *Massive* eruptions of foci into main lymphatic trunks or veins provide the setting for generalized miliary tuberculosis. Pulmonary tubercles, sending bacilli to pulmonary veins, originate new foci in the other viscera and parts of the body supplied by the systemic arteries. Visceral passages spread infection to other parts of a viscus or to other viscera that are in communication with it—lung to intestine, kidney to bladder, etc.

We must imagine also that bacilli may be carried out of tubercles, even though no real ulceration has occurred, and into lymphatics, blood-vessels, and visceral ducts. This must happen when tubercles are in apposition to these pathways, and when, at the same time, their fibrous investments are loose, open, and thin; or finally, when they are undergoing central necrosis. No doubt many of the more isolated foci of metastasis are set up under these conditions; the number of bacilli extruded at any one time is relatively small.

Tubercles, also spread by direct extension, or bacilli may be carried through their envelopes and then proceed by short excursions along lymphatics, to lodge nearby and there set up fresh tubercles. The same result may also follow when actual ulceration permits eruption into the tissues and not into a channel of dissemination.

Summary.—This account has aimed to set forth the more general and elementary principles underlying the formation of anatomical changes set up by tubercle bacilli when infection occurs and after it has been established. By the processes of proliferation, exudation, necrosis, and repair in variable proportions are built up all the manifold pathological lesions that are certainly caused by the tubercle bacillus. Proliferation is the native reaction

of tissues to the bacilli; it is rather slow and indolent and, until it is well under way, allows the spread of bacilli. Inflammation or exudation is a type of reaction (allergy) that is conferred by infection; it is prompt, and tends to fix bacilli and prevent their spread from the first. Proliferation gives rise to discrete and circumscribed processes; inflammation, to diffuse processes. After the first few days all changes brought about by *tubercle bacilli* possess characteristics of both types of reaction.

Allen K. Krause.

ACUTE MILIARY TUBERCULOSIS

Acute miliary tuberculosis is brought about by a sudden seeding of the body with large numbers of virulent tubercle bacilli. There may be only one such seeding or several at intervals.

To Buhl (1856) belongs the credit for the conception that miliary tuberculosis is a form of sepsis directly comparable to that dependent upon a focus of pyogenic bacteria; that just as metastases result from a primary focus of Staphylococcus aureus, so do they from the arrival in the blood- or lymph-stream of large numbers of tubercle bacilli.

In 1877, even before the tubercle bacillus had been demonstrated, Carl Weigert established the relationship between acute miliary tuberculosis and the caseous focus occurring in a vein or large lymph-vessel. He showed how a vascular tubercle may be the source from which the blood receives an acute inpouring of tubercle bacilli. It was his belief that following a periangitis there is an extension of the tubercle from without the vessel inward to cause the formation of tubercles in the intima of the vessel. Benda maintained that the tubercles develop of themselves in the intima of the vessel through lodgment of bacilli carried in the circulation from time to time; these tubercles become caseous and empty their bacilli into the vessel current. Subsequent investigations have indicated that both views are correct.

Since Weigert, sufficiently careful search has revealed the presence of a vascular tubercle as the portal of massive blood infection in the great majority of cases. Such a tubercle may be located in a vein, in the thoracic duct, in an artery, or in the heart itself.

Astley Cooper in 1798 first described tuberculosis of the thoracic duct. Subsequent observers have found it a frequent source of bacilli in miliary disease, but decidedly less often than tuberculosis within the lung veins. A résumé of the work done by the leading German pathologists from 1882 to 1892, covering 394 cases of acute general miliary tuberculosis in which the portal of infection was found, shows the veins of the lung or the thoracic duct to have been responsible in 345 cases; the veins in the lung were to blame in 210 of these, or more than one-half, and the thoracic duct in 135 cases, or about one-third. The remaining 49 cases were due to involvement of veins elsewhere than in the lungs, to tubercles in the heart and in the arteries. While bacilli may break into an artery in large numbers, this event is relatively quite rare, and the resulting miliary disease is restricted to that area of the body supplied by the particular artery invaded.

The infection in acute general miliary tuberculosis is always blood borne. Obviously this statement applies to bacilli from thoracic duct tubercles, whence the bacilli are carried directly to the right heart. There are cases

of serous membrane tuberculosis brought about by direct lymph-stream infection, but these are not to be regarded as acute general miliary disease.

The pathological changes depend upon the quantity of bacilli discharged, whether they invade the blood-stream at one time or at intervals, the site of invasion, and the unknown factors of bacterial virulence and individual susceptibility. The lungs naturally bear the brunt of the attack of all bacilli coming from the thoracic duct and the veins of the body, while infection which breaks into the veins of the lung is delivered to the left heart and general circulation, including that of the brain. Weigert divides the cases into three groups: (1) The acute general miliary form in which practically all the organs are heavily infected. (2) A form in which there is only a small number of tubercles in one or several organs. (3) The form more commonly found in children in which the tubercles are widely distributed, more chronic in nature, and characterized by greater tendency to caseation. The following description is of the first of these forms, the clinical syndrome known as acute general miliary tuberculosis.

Clinical Forms.—There are certain outstanding symptom-complexes which serve as a basis for classifying acute general miliary tuberculosis. Naturally, many cases fall between these groupings, while others change from one to another, or show phases of more than one group.

There are three chief forms into which the great majority of cases of miliary tuberculosis fall: the typhoid form, so-called from its resemblance to typhoid fever; the pulmonary form, named from the predominance of its lung symptoms; and the meningitic form, with its pronounced involvement of the meninges. There are also subacute cases and still another group long known to the French as the typho-bacillose of Landouzy.

The figures of Reinhold give an idea of the relative frequency of the different forms. Among 96 cases there were 12 of the typhoid variety, 12 of the bronchopulmonary, and 56 of the meningitic type. Whenever children are included in the figures the meningitic form always preponderates.

Typhoid Form.—The onset is usually gradual, with increasing prostration and fever, anorexia, headache, and rarely nosebleed. The patient becomes more and more prostrated, the pulse increases in frequency and tends to be rapid, out of proportion to the fever. Respirations are usually increased from the outset, and as the disease progresses dyspnea and cyanosis develop. There are frequently the mild delirium and the psychoses which are also seen in typhoid fever. Splenic enlargement occurs, but is marked only in children. There may be diarrhea and distention, and even slight intestinal bleeding. The fever tends to be irregular, 102° to 104° F. in the evening and 99° to 100° F. in the morning. The inverted type of fever may occur, and a few cases have been reported in which fever was lacking entirely. A hemorrhagic rash is seen now and then, roseola-like in character, but not appearing in crops and usually not difficult to differentiate. The tongue is dry. The blood shows more often a slight leukocytosis, but leukopenia occurs sufficiently often to render the total white cell count of comparatively little value. On the other hand, there is practically always an increase in polymorphonuclears at the expense of the lymphocytes. Many observers contend that a definite lymphocytosis speaks definitely against miliary tuberculosis.

The presence of bacilli in the circulating blood is still a matter of controversy. Certainly they are there at times, but how frequently is still dis-

puted. The reliable method of determining their presence is the inoculation of a guinea-pig, a procedure which often requires too much time to render it of clinical value.

The urine usually shows some albumin; the diazo-reaction is generally positive. Tubercle bacilli may be found.

The demonstration of miliary tubercles in the choroid is of great diagnostic value. They are usually located toward the periphery of the retina, thus necessitating good dilatation of the pupil. They should be sought daily and by one skilled in ophthalmoscopy. Under such conditions they are found in more than 50 per cent. of cases.

Diagnosis.—Very frequently this form of miliary tuberculosis is discovered only at autopsy, which is evidence of the difficulty often encountered in its diagnosis, but if it is kept in mind mistakes occur less often. The temperature curve is usually more irregular than that of typhoid fever; the pulse is more rapid and the dyspnea and cyanosis are marked. The history of the case is of great importance, especially as to evidence of already existing tuberculosis. The blood is sterile except for the possible presence of tubercle bacilli; there is a polynucleosis often without any leukopenia; and there is no agglutination of typhoid bacilli unless agglutinins persist from an earlier typhoid fever or from prophylactic vaccination against the disease. Most important of all, however, is the *x*-ray examination of the lungs, which often gives the clue to the diagnosis at a relatively early date. Obviously, other forms of sepsis also have to be eliminated.

Pulmonary Form.—Here the seeding of the lungs with miliary tubercles and the accompanying collateral inflammation bring about an accentuation of objective and subjective pulmonary symptoms. Respiration and pulse rates, which are rather high in the beginning, tend steadily to increase until dyspnea and cyanosis are present out of all proportion to the physical signs. This combination in itself should make one suspicious of miliary disease. The temperature tends to be remittent and is not necessarily very high. The physical signs are those of a bronchitis with possibly scattered areas of dulness and moist râles. Sputum may or may not be present and is generally not purulent until later in the disease. The air-hunger increases, emaciation is extreme, the mind becomes hazy, and death takes place with edema of the lungs and collapse. Usually the condition lasts about one month, but the duration may be shorter, or it may prolong itself to three or four months. Children show the picture of a capillary bronchitis, and one should be particularly on guard if such a condition follows measles or pertussis. In elderly people the disease runs an atypical course and is generally diagnosed only at the autopsy table.

The *x*-ray shows the typical shadows, usually by the end of the second week, but this is not necessarily true, and another two weeks may pass before the picture is clear.

Meningeal Form.—*Tuberculous Meningitis.*—This form is found particularly in children and makes up the great part of tuberculous meningitis of this period of life. Strictly speaking, it should be distinguished from the pure form of tuberculous meningitis, but the differentiation generally presents great difficulties. Only when this true form is obviously a direct lymph-borne infection, as in extension from a neighboring tuberculous bone, are the two forms readily separated.

Robert Whyte in 1768 was the first to obtain accurate knowledge of this

condition. Guersant in 1828 observed the tubercles, and his pupils attributed this so-called granular meningitis to tuberculosis. Papavoine in 1830 demonstrated the relation of the meningeal tubercles to tubercles elsewhere; Rilliet and Barthez described the symptomatology, as did also W. W. Gerhard, of Philadelphia, to whom Osler gives credit for having placed the disease upon a firm anatomical and clinical basis.

To what extent this form preponderates in children is brought out in Steinmeier's statistics from Fraenkel's Pathological Institute at Hamburg. Among 186 autopsies of children under fifteen years of age, acute miliary tuberculosis without associated tuberculous meningitis was found only 6 times, whereas tuberculous meningitis was present in 69 cases, in 15 of which it was associated with acute miliary tuberculosis, and in 21 cases with chronic disseminated tuberculosis. Among 1119 autopsies of adults acute miliary tuberculosis was found 26 times without tuberculous meningitis; there were 63 cases of tuberculous meningitis, of which 11 showed acute miliary tuberculosis and 13 chronic disseminated tuberculosis.

Morbid Anatomy.—Tuberculous meningitis is essentially a basilar meningitis, in contrast to the acute pyogenic forms of meningitis. The lesions occur particularly in the regions of the circle of Willis, the interpeduncular space, the fissures of Sylvius, and the optic chiasma. There is usually a turbid fibrinopurulent exudate about the structures of the base and the pia mater is thickened.

Along the arteries, especially those of the Sylvian fissures and their branches, there are characteristic groups of small tubercles bathed in exudate. The underlying cerebral tissue is also affected and is congested, edematous, and softened, with minute capillary hemorrhages. Lesions are also frequently found in the ependyma of the ventricles. The ventricles themselves are usually distended with fluid, a condition which plays an important rôle in the symptomatology. As a rule, the tubercles are recognizable on simply removing the brain from the skull, but in some instances they may be very difficult to find. The arteries of the anterior and posterior perforated spaces, the middle cerebral arteries, and their branches should be carefully searched with a lens against a proper background.

There is a characteristic association of inflammatory lesions with the tubercles. The arachnoid is more or less opaque, the pia is thickened, congested, and dotted with small punctate hemorrhages.

The cord is always involved, but the lesions are usually fairly discrete and often there is only a congestion. Tubercles of the cord, when they occur, are usually located in the posterior portions and in the lumbar region.

Symptoms.—The polymorphism of the clinical picture of tuberculous meningitis is well known. It is due to the variance in the type of lesions, the difference in their location, the extent of involvement of the cortex, and the degree of hydrocephalus.

First there is the prodromal period, the onset of which is almost always gradual and insidious, with such symptoms as loss of weight and strength, evening fever, and digestive trouble. Later there may develop change of character, inattention, poor memory, headache, and insomnia. This period may last weeks or months, with remissions in the symptoms, at times to their complete disappearance.

The second is the period of actual onset, with its very important triad of vomiting, headache, and constipation. The vomiting is apparently

without cause and bears no relation to eating; the headache is intense, with exacerbations which cause the child to cry out suddenly. Constipation is less constant, but when present it stubbornly resists treatment. A marked feature is the absence of accompanying tympanites.

These symptoms are not pathognomonic and by themselves do not constitute a diagnostic complex. Fever appears in this stage, remittent, rising to 102° to 103° F. The pulse is 90 to 120. The child is prostrated and restless.

Finally, there is the period of established illness with its multiplicity of symptoms and signs. The child is stuporous, prostrated, lies on its side, with face turned from the light. It resents interference of any sort and is strongly inclined to sleep. This somnolence is a striking feature and continues up to the end. There are remissions, however, almost always with mild delirium, loquacity, stereotyped movements, and from time to time the sudden hydrocephalic cry.

Motor symptoms include convulsions, which are rarely general except in very young infants. More often they are localized. They occur in the muscles of the eyes—nystagmus, intermittent strabismus, alternating myosis, and mydriasis. The third nerve is particularly apt to be affected. Again the muscles of the face are involved, with grimacing, grinding of the teeth, and sucking motions.

The muscle contractions are signs of equal or even greater importance. Stiffness of the neck occurs early and must be elicited gently. It rarely attains the extreme degree observed in ordinary cerebrospinal meningitis. With stiffness of the neck there is associated a contraction of the muscles of the trunk and lower limbs. This is demonstrated by the Kernig sign, which is, however, not constant, and, when present, is less marked than in the forms of purulent meningitis. The contralateral reflex sign of Brudzinski is also of value. If one leg be flexed with the thigh against the abdominal wall, the other leg should undergo flexion or hyperextension. This sign is less constant than the Kernig. Brudzinski has more recently described another sign—the cheek phenomenon. If pressure is exerted on both cheeks just underneath the zygoma, there is a reflex upward jerking of both arms, with simultaneous bending of the two elbows.

Paralyses are usually temporary, often following convulsions, but permanent palsies may occur, particularly toward the termination of the disease.

The reflexes are always hyperactive in the presence of contractions, diminished or absent in the presence of paralysis. Hyperesthesia—cutaneous, ocular, and aural—is frequent. Vasomotor irregularities are common.

Diagnosis.—The diagnosis of tuberculous meningitis is usually made without much difficulty. The history of the case or the presence of tuberculosis elsewhere in the body usually afford a good clue, while the examination of the cerebrospinal fluid generally settles the question. The fluid is clear, as a rule, but may be very slightly cloudy if an unusually large number of cells is present. In most cases a cobweb-like clot of fibrin forms in the course of twelve to twenty-four hours, and in it the tubercle bacilli are most apt to be found. If the searcher be skilful and patient the bacilli are found in almost 100 per cent. of cases. Hemenway, at the Babies Hospital in New York, had practically this result. The cell content of the fluid should be determined before the clot has formed. White cells are present to the

extent of 25 to 1000 or even higher per cubic millimeter. They are largely lymphocytes, although in exceptional cases the percentage of polymorphonuclears may be 50 per cent. Fortunately, in this latter group tubercle bacilli are present in relatively large numbers, and a meningitis due to pyogenic bacteria can thus be excluded. Albumin and globulin are practically always present.

Anterior poliomyelitis and lethargic encephalitis may present great difficulties of differentiation because both may show a mononucleosis and positive globulin in the spinal fluid. It may require more than one lumbar puncture for the finding of tubercle bacilli, and the case may have to be observed for some time in these instances. In young children a positive von Pirquet reaction may throw light on the case, and tubercles of the choroid are to be sought when special difficulties of diagnosis arise.

Prognosis.—In no disease is the prognosis more hopeless. There are, however, a number of authentic cases of recovery in the literature. One of the most recent lists published was that of Cramer and Bickel, who found 45 such cases, all of them with positive findings of bacilli in the cerebrospinal fluid either by direct examination, by guinea-pig inoculation, or by both methods.

Treatment.—Nothing avails except to palliate symptoms. Lumbar puncture may be employed frequently if it relieves headache and nervous irritability.

Subacute and Chronic Forms of Miliary Tuberculosis.—On account of the differing conditions attending the development of miliary tuberculosis it not seldom happens that cases, instead of progressing to an early termination, drag on for long periods as chronic cases. The patient may improve in every way, even for several months, only to succumb eventually.

Typhobacillosis of Landouzy.—This form, originally described by Landouzy in 1882, is much like the above described typhoid form, but rather less severe in its manifestations and distinguished by the fact that the patient often makes a partial recovery. After the subsidence of the typhoid-like symptoms the patient becomes convalescent, but not frankly so. The appetite continues impaired and the emaciation persists. As Landouzy states, these patients almost always recover from their fever, but harbor tuberculosis in a quiescent form. The latter unmasks itself somewhat later. There are other forms of this so-called typhobacillosis—a slowly progressive form with recrudescences; a subacute septicemia; and an attenuated form with digestive symptoms predominating. Such conditions should always be borne in mind in cases of unexplained fever.

TUBERCULOSIS OF THE LYMPHATIC SYSTEM

Although the rôle of the lymphatic system in tuberculosis has always been recognized as important, interest in this phase of the subject has lately been considerably increased. Tubercle bacilli, to obtain entrance to the body tissues, must almost always lodge first upon some mucous membrane of the nose, throat, lungs, or intestines. The infection may be initiated in these tissues, but usually the bacilli pass without causing disturbance into the lymphatic system. They are ingested by phagocytes (the macrophages and the polynuclear leukocytes) and are carried along in the lymph channel. Krause admirably describes how they pass to one node and then another, becoming localized here or there, or being carried into the venous system

through the thoracic duct or the shorter lymphatic trunks which lead directly into the veins. Every lymph-node is at a converging point and tends to collect any foreign material in its field of drainage. From the periphery to the interior of the body tubercle bacilli first follow the lymphatic paths, and, consequently, lymph-nodes are generally the first tissue infected and are often the seat of the most advanced lesions.

For many years the term *scrofula* was applied to tuberculosis of the lymph-glands as well as to syphilitic infections, which at that time could not always be distinguished from tuberculous infections. For the most part, however, it was applied to tuberculosis of the cervical glands. Clinicians noted that there were surprisingly few cases of pulmonary tuberculosis in which a history of scrofula was obtainable, and even as early as 1886 Marfan stated that one almost never finds progressive pulmonary tuberculosis in individuals who have had suppurative cervical adenitis and been cured before the age of fifteen years, and in whom no other foci of tuberculosis are demonstrable. This is explained by the fact that the immunity conferred by such relatively mild infections is sufficient in most cases to cope with subsequent infection, provided the latter is not too great and no accident causes a discharge of the contents of the node into the general circulation.

Tuberculosis of the Cervical Glands.—Cervical gland tuberculosis is practically never seen in children less than one year of age and usually not in those less than three years old. The incidence is highest between the ages of seven and ten. Bacilli enter through the buccal, pharyngeal, and nasal mucosa, especially via the tonsils, or from skin lesions of the face which drain into the cervical glands. Mitchell, of Edinburgh, who has studied the relation of the tonsils to tuberculous cervical adenitis, has reported a series of 106 cases, 100 in children of all ages up to fifteen years, and 6 in adults. The excised nodes and also the tonsils were examined to establish the tuberculous character of the infection. Forty-one (38 per cent.) of the 106 cases showed undoubted tuberculous lesions in the tonsils. From these data Mitchell concludes that tonsillectomy is essential in all tuberculous cervical adenitis in children.

Park and Krumwiede in 1912 made a thorough study of the relation of the bovine type of tubercle bacillus to tuberculous cervical adenitis, and found infection by the bovine type of bacillus in 61 per cent. of patients under five years of age, in 38 per cent. of those between five and sixteen years of age, and in 2.7 per cent. of adult patients. These figures indicate clearly that tuberculous adenitis is a *food* and *mouth* infection. As Calmette remarks, these glands become involved while the child is handling everything and putting many articles in its mouth. Previous sensitization by an earlier infection, usually in the tracheobronchial glands, is very apt to have taken place. An explanation of the differences in the course of these infections is probably to be found in the quantity and frequency of infection. If the new infection be sufficiently large or repeated, swelling develops rapidly and is followed by caseation, softening, and discharge. With smaller dosage, on the other hand, the glandular swellings do not attain any great size and in time become fibrotic and regressive.

The upper set of deep cervical nodes are most frequently the first involved, but infection of the submaxillary glands is only slightly less common. In 80 of Mitchell's 106 cases the disease was most advanced in the tonsillar nodes at the junction of the common facial and internal jugular

veins. The parotid group, submental and pre-auricular, may occasionally be the first attacked. Usually the entire chain of nodes is affected, involvement being less complete the farther the gland is from the site of infection. The disease may affect the supraclavicular and even the axillary nodes.

Suppuration occurs in a fairly large proportion of cases, and evacuation of the pus, whether spontaneously or as the result of some surgical procedure, causes the inflammation to subside. The disease is often protracted, and may extend over three or four years. With the approach of puberty it tends to disappear.

Modern treatment is devised to remove the source of infection—most often the tonsil. Excision of the nodes, so extensively advocated ten or fifteen years ago, is less desirable than heliotherapy and *x*-ray. Of prime importance, no matter what the form of local treatment, is recognition of the fact that all tuberculosis must be treated as a systemic infection. This allows the patient to be given every opportunity to build up general health.

Tuberculosis of the tracheobronchial lymph-nodes occurs particularly in infants and children. In infants dying of tuberculosis the tracheobronchial glands are almost invariably diseased, and one may almost say that tuberculosis does not occur in infants without involving these glands. The primary focus of tuberculosis in infants is usually pulmonary, and infection of the tracheobronchial nodes is secondary to the initial tubercle formation in the lung. Presumably the patency of the lymphatic channels in the infant and the relative lack of resistance account for the frequent massive infection of the tracheobronchial nodes and their caseation. The softening of these glands so frequently leads to rupture into important vessels that the prognosis has in the past always been regarded as particularly serious. In more recent years, however, careful tuberculin tests on infants subjected to known but not unduly severe exposure have indicated the presence of an infection which may well be thrown off if contamination has not been too great and if the child can be kept in a healthful environment away from further infection.

These glandular enlargements may attain considerable size and produce various symptoms of pressure because of their proximity to important vessels and nerves. Pressure upon the vagus or recurrent laryngeal nerve may cause dyspnea and paroxysmal and often severe and prolonged coughing which simulates whooping-cough, croup, and asthma. The dyspnea may be quite severe. Pressure upon the superior vena cava produces cough, dyspnea, cyanosis, and puffiness of the face, even to edema. Ulceration into one of the large vessels or bronchi is a less common occurrence. The glands extending out from the hilum and along the bronchi may caseate and spread the disease by continuity into the lung and pleura.

In individuals more than about four years old tuberculosis of the tracheobronchial glands assumes a different aspect and caseation becomes progressively less frequent. It is in these glands, however, that the disease is most apt to smoulder during childhood. Symptoms may vary from none at all to those of marked toxemia. Usually there is malaise, anorexia, malnutrition, anemia, and low-grade afternoon or evening fever. The child appears tubercular, but the physical signs of localized disease are difficult to demonstrate. Very few pathological conditions of such importance produce so few definite physical signs. The few that are to be found depend largely on the size of the involved nodes. There may be dulness under the upper

sternum or behind in the interscapular space between the third and seventh dorsal vertebræ; or there may be evidence of pressure, but generally these signs are lacking. The *x*-ray should permit easy positive diagnosis, but the numerous large structures in the region of the glands prevent this. Interpretation of shadows about the hilum of the lung is difficult, and often the best qualified radiographers cannot definitely determine diagnosis. At times, on the other hand, the *x*-ray diagnosis may not be so difficult. The tuberculin test, preferably the intradermal, should be employed in all doubtful cases, since in our American cities the incidence of positive reactions is considerably lower than in Europe.

Tuberculosis of the Mesenteric Lymph-nodes.—In tuberculosis of the mesenteric lymph-nodes the mesenteric and retroperitoneal glands enlarge and often caseate, particularly in children. Suppuration and calcification may also take place. John Thomas has found that the occurrence of such conditions among tuberculous children in New York, Philadelphia, and Boston was considerably less common than in England or on the European continent (one-third to one-fifth). Although they comprised 1.6 to 1.13 per cent. of over 60,000 cases of children's diseases reported from European cities, they constituted only 0.14 to 0.42 per cent. in the American cities. Recently Opie has reported the results of autopsies of 90 children and 50 adults made in St. Louis in 1917 in which not a single case of healed mesenteric tuberculosis was found. This result was in marked contrast to his experience during the war at Rouen, where he made a special study of 66 young male adults, all British soldiers, with few exceptions between twenty and thirty years of age. Caseous or calcified mesenteric nodes were found in 18 instances. Fifteen other autopsies on similar subjects gave practically the same results. These men with one exception died of conditions wholly unrelated to tuberculosis. The higher incidence of tuberculosis among cattle in Great Britian was advanced to explain these results. It was noteworthy that in these soldiers with tuberculosis of the mesenteric glands focal pulmonary tuberculosis was scanty or absent.

Tuberculosis of the mesenteric lymph-nodes is almost always due to entrance of infection through the intestinal tract with or without production of a demonstrable lesion. The more carefully the lesions are sought, the more frequently they are found in the intestinal mucosa. The bovine bacillus in milk plays a considerable etiological rôle. In 1912 England, Germany, and New York City showed approximately the same percentages of bovine bacillus infection of the mesenteric glands, about 14 per cent. in adults, 57 per cent. in young children, and 47 per cent. in children under five years. Recently, however, W. H. Park, who has directed the investigations in New York, reports a marked decrease of bovine infection due presumably to pasteurization of milk.

The SYMPTOMS of this condition are emaciation and debility, anemia, diarrhea with watery stools, and moderate fever. The abdomen and intestines are usually so distended that glandular masses cannot be felt. Frequently the peritoneum is involved, and the signs and symptoms of tuberculous peritonitis are added to the syndrome.

In TREATMENT, heliotherapy and ultraviolet rays are very helpful when employed as an adjunct to the accepted hygienic treatment.

Generalized Tuberculous Adenitis.—Although in many cases of tuberculosis careful search would reveal the presence of a few tubercles in the

lymph-nodes, there is a special form of the disease in which the lymph-nodes throughout the body are practically the only seat of infection. This is rare, and generally confused with Hodgkin's disease, from which differentiation is sometimes impossible without biopsy. The glands most affected are the bronchial, mesenteric, and retroperitoneal, but those in the neck and axilla may also be strikingly involved. The lymph-nodes become caseous and matted together in packets. There is almost always fever, and the temperature may be considerably elevated. The course of the disease is usually subacute or chronic until death results from cachexia or extension of the infection to other organs.

TUBERCULOSIS OF THE MAMMARY GLAND

Mammary gland tuberculosis is not at all common, but does occur from time to time. It must be considered in the diagnosis of any mass in the breast. The lesions manifest themselves as small hard nodules which may become caseous, break down, and lead to the formation of fistulæ, like tuberculous fistulæ elsewhere. These discharge a thin pus in which tubercle bacilli can often be found. According to Birch-Hirschfeld, tuberculosis of the mamma seldom occurs except when there is extensive tuberculosis of other organs; it is very often accompanied by tuberculosis of the corresponding axillary glands.

The path of infection is still open to question. Although the milk ducts are more often the seat of the earliest and most extensive change, the disease may occur in women who have never been pregnant, and it is questionable whether tubercle bacilli can be excreted by the milk ducts. The infection may enter the breast by the blood-stream; or it may gain entrance by the lymphatics through the chest wall from the pleura, a phenomenon which would indicate a retrograde lymph flow the opposite of that associated with cancer of the breast.

TUBERCULOSIS OF THE CIRCULATORY SYSTEM

Heart.—Tuberculosis of the heart of sufficient severity to produce clinical symptoms is an extremely rare condition, but the pathologist occasionally encounters tuberculous lesions in the heart at autopsy. The miliary tubercles associated with general miliary tuberculosis may be found, or one or more tuberculous nodules, or perhaps a proliferative myocarditis in the vicinity of a tuberculous focus. It is reported that a tubercle of the myocardium may become caseous, undergo necrosis, and break through the endocardium to produce general miliary tuberculosis. Endocarditis was found 151 times in the 11,000 autopsies on tuberculous subjects by G. W. Norris. In practically every case, however, the presence of other bacteria rendered absolute diagnosis difficult.

Arteries and Veins.—Both arteries and veins may become involved during pulmonary tuberculosis, but only rarely. In the miliary type of the disease tuberculous nodules may develop within the vessel walls, and in a few cases tubercles have been said to form within the aorta. In the lungs periarteritis may extend from without inward and lead to thrombosis; or caseous softening may spread through the wall of the vessel until an aneurysm forms; or the vessel may rupture and produce hemoptysis.

TUBERCULOSIS OF THE SEROUS MEMBRANES

General Tuberculosis of the Serous Membranes (*Polyserositis*).—General tuberculosis of the serous membranes is an unusual, blood-borne infection which becomes localized because of local susceptibility. Usually the peritoneum and pleura are simultaneously involved; occasionally the pericardium is also infected, and more rarely the joints and meninges. In the pleura and peritoneum the disease may be acute or chronic. Effusion usually takes place in both cavities. The tubercles themselves are fibrous, or caseous and ulcerative. The type in which there is little or no exudation and the membrane is merely thickened is more difficult to recognize.

Tuberculosis of the pericardium is probably more common than is generally thought. Norris is said to have seen the condition in 82 out of 1780 autopsies on tuberculous patients, and German statistics reveal an even higher incidence—3 per cent. of examinations of tuberculous children. Pericardial infection, except that of the miliary type, is almost always secondary to tuberculosis of the neighboring mediastinal glands, pleura, or peritoneum.

The lesions may be of the miliary type, or associated with effusion or the formation of adhesions. In pericardial tuberculosis with effusion the membrane is thickened and hemorrhagic. There is often a sort of false membrane with tubercles underlying it. The exudate itself may cause considerable enlargement of the heart, which is demonstrable both by physical and *x*-ray examination. The fluid is clear, cloudy, or hemorrhagic. When adhesions form the heart becomes enlarged and signs of adherence of the pericardium appear. At times the adhesions are very thick.

Antemortem *diagnosis* of pericardial tuberculosis is rare. The *prognosis* is always grave.

Tuberculosis of the pleura is of great importance and interest because it often masks pulmonary tuberculosis. In order to safeguard the patient, therefore, pleurisy, both with and without effusion, should always be considered tuberculous until proof to the contrary has been obtained. Tuberculous pleurisy is almost always a secondary infection, a reinfection, or the reactivity of an old, latent infection which may date back to childhood. At times the source of the organisms in the pleural membrane is readily demonstrable, when, for example, a focus is immediately subjacent in the pulmonary tissue. More often, however, the bacilli are carried in the lymph from foci elsewhere or in the blood-stream, as in the acute miliary type. Thus the real cause is the mobilization of tubercle bacilli and their localization in the pleura, although a number of other factors, such as the anergy-producing diseases, exposure, trauma, etc., play a rôle.

Tuberculosis of the pleura may be of the *acute, transitory type*, with a dry lesion or exudation of a serofibrinous or hemorrhagic fluid. Such forms may be cured clinically and at times anatomically as well. When the lesions lie dormant, as they often do, there is danger of a subsequent attack or definite involvement of the pulmonary tissue. There is also a *chronic form* in which the lesion resembles that of tuberculosis in other parts of the body. The effusion of serofibrinous, bloody, or even purulent material does not subside, and adhesions and encapsulations may cause dense thickening of the pleural sac. In still another rare type of the disease there is slow, *progressive formation of dense adhesions*, a process not unlike that of chronic pulmonary fibrosis. *Generalized infection of the pleura* may be

derived from the blood and produce miliary changes similar to those found in other tissues.

Paterson's experiments seem to indicate that virulent tubercle bacilli which reach a pleura sensitized by tuberculosis elsewhere in the body encounter the reaction of acute superinfection in the pleural cells. If the pleura is free, this is evidenced by *exudation* of serofibrinous material when the infection is not severe; by the production of hemorrhagic fluid when the organisms are more abundant. Such a reaction is doubtless defensive, particularly in the idiopathic type of the disease. It frequently appears to immunize and benefit the patient in a manner not entirely explained on mechanical grounds. While not often associated with chronic pulmonary tuberculosis, this exudation does occur from time to time, and may initiate a definite improvement after subsidence of the acute pleuritic symptoms. The lesion of *adhesive pleurisy* is more protective in character, its function being to prevent ulceration of the underlying pulmonary lesion through the visceral pleura, and the consequent spontaneous pneumothorax.

The SYMPTOMS vary with the pathology, but practically always in tubercular pleurisy there is the constitutional response characteristic of other types of tuberculosis. Pain is a common symptom usually located over the lesion, but sometimes referred elsewhere. The diaphragm is frequently involved and the pain referred to the shoulder and abdomen in such a manner as to be misleading. The onset of exudation is apt to end the pain. Examination of the fluid is of great diagnostic value, the usual characteristics being the slight cloudiness and the brownish-yellow or amber color, with perhaps a greenish tint. The fluid may have a reddish tinge if many erythrocytes are present. A jelly-like clot forms on standing. The specific gravity varies from 1012 to 1024, and albumin is present (40 to 60 gm. per liter), these two latter facts establishing the fluid as an exudate instead of a transudate. The cystology is important; the cells in the relatively clear fluid consist of red blood-corpuscles, polymorphonuclear leukocytes, large mononuclear cells and lymphocytes, the latter far outnumbering the others. Tubercle bacilli are present, but are very difficult to demonstrate except by inoculation of guinea-pigs. The larger the quantity of fluid injected into the guinea-pig's peritoneum, the better are the chances of infecting the animal. When the pleural fluid is purulent tubercle bacilli are often readily found in ordinary smears. The material examined should be taken from an ulcerative area, usually situated in the lung itself.

PROGNOSIS.—Tuberculous pleurisy may terminate in complete and permanent arrest; may recur after some time; be followed by pulmonary tuberculosis, or continue as chronic pleurisy without absorption of fluid and with marked thickening of the pleura.

TREATMENT.—While usually a benign infection, tuberculosis of the pleura must be treated like tuberculosis of other tissues to prevent the possibility of its development into more inherently serious conditions.

Tuberculosis of the peritoneum also involves a serous membrane and in many ways resembles tuberculous pleurisy, with which it is at times associated. Like pleurisy, it is a secondary disease, a phenomenon of superinfection often considered primary because the original focus of infection remains latent. Consequently, it does not occur in infancy, but develops during late childhood, puberty, or early adult life.

The peritoneum may become infected by rupture of a caseated lymph-node into the circulation, with extensive studding of the whole serous membrane. More often, however, a number of bacilli are discharged into the peritoneal cavity from some caseous gland, one of the mesenteric, iliac, or diaphragmatic nodes, for example. The reaction may be distinctly fibrous, with a marked tendency to mat the intestines together by adhesions; ulcerative and caseous, with the formation of more massive lesions which tend to caseate and ulcerate; and, most important of all, exudative, and not unlike pleurisy with effusion. The latter type is associated with a tendency to form scars and contractions. The fluid is serofibrinous, sometimes rather hemorrhagic, and often pocketed off by adhesions; the quantity is not so great as in hepatic cirrhosis, but may, nevertheless, be fairly large. Frequently the omentum becomes thickened in a transverse band in the upper abdomen which is palpable and not unlike a tumor.

Symptoms.—The symptoms are very irregular in character. The onset may be sudden, with severe abdominal symptoms of such severity as to lead to operation for various disorders. Diffuse infection of the peritoneum may occur with or without exudation. If fluid is present it may be free at first, only to become encapsulated later, and be no longer movable on change of position. Localized sacs of fluid may resemble tumors (ovarian cysts) or the fluid mass may suggest that associated with disease of the fallopian tubes. The plastic infection with its resulting adhesions may also simulate a tumor. The presence of sacculated fluid adds great difficulty to diagnosis. Tympanites, which may be due to lack of intestinal tone, adhesions, or compression, is often troublesome. Fever is common.

Diagnosis.—Examination of the fluid throws much light on its cause. In tuberculous peritonitis the specific gravity is above 1015, and endothelial cells, red blood-corpuscles, and particularly lymphocytes are present. Tubercle bacilli may be found without guinea-pig inoculation, although usually such a test must be employed for their demonstration.

Prognosis.—There is nothing typical about the course of tuberculous peritonitis. The disease may progress rapidly or undergo improvement. Experimental work on superinfection will probably go far to explain the variations in the form of the disease. The peritoneal response, for example, differs greatly with the size of the superinfecting dose of bacilli and with single or repeated doses. Tuberculosis of the peritoneum, like that of other serous membranes, may heal spontaneously, and it is probable that both the disease and spontaneous cure are much more common than is generally supposed.

Treatment.—As long ago as 1884 it was demonstrated that simple laparotomy at times cured tuberculous peritonitis, but since that time the usefulness of such treatment has been much questioned. Certainly tuberculous peritonitis tends markedly to disappear spontaneously, and should be given every chance to do so before laparotomy is performed. More recently there has been advocated the method of evacuation of a serous peritonitis and replacement of the fluid by oxygen. The apparatus employed in the treatment of the lung by artificial pneumothorax can be used to advantage, but is not necessary. Although there are still relatively few reported cases in the literature of this country the number is constantly increasing and the results are notably good. Some successfully treated cases have also been reported abroad, and it would seem that this more con-

servative method should always be tried before resorting to laparotomy. Garbat gives a bibliography of both foreign and American reports on this form of treatment. When other measures have failed, particularly in cases with effusion, one may resort to incision. The acute disease should be treated like other tuberculosis, with rest and hygienic care, laparotomy being employed only when there is definite need for surgery, and aspiration when the quantity of fluid is excessive. As the condition becomes more chronic heliotherapy and quartz light therapy play an important part. With increasing knowledge of these latter forms of treatment as supplements to rest and general care, the results of medical treatment have constantly improved.

Willard B. Soper.

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PULMONARY TUBERCULOSIS

Tuberculosis of the lungs manifests itself chiefly as a *chronic disease*, with occasional or frequent exacerbations. It may, however, appear in an *acute form* which runs a rapid and usually fatal course. The former type of the disease is very common, the latter comparatively rare.

When acute, the disease usually takes the form of pneumonia. If lobar in type, it is spoken of as *acute tuberculous pneumonia;* when lobular, as *acute tuberculous bronchopneumonia.*

There are various forms of *chronic pulmonary tuberculosis*, which may be grouped conveniently under two general headings: *chronic ulcerative tuberculosis*, by far the commonest form; and *fibroid tuberculosis.*

Infection of the lungs by the *tubercle bacillus* may take place by means of the bronchi, lymphatics, or blood-stream. The acute forms of pulmonary tuberculosis are usually bronchogenic in origin, while in the chronic forms infection may spread through any or all three channels.

Acute Pneumonic Tuberculosis of the Lungs

The tubercle bacillus may cause pneumonic consolidations which in the early stages are identical with the lobar and lobular consolidations produced by such organisms as the pneumococcus. These consolidations occur only when the pulmonary tissues have been sensitized by a previous tuberculous infection and are the most marked manifestations of the allergic reaction occurring in the disease. The sensitized lung is flooded with tubercle bacilli, rarely through vascular channels, usually by aspiration of infectious material. This material may come from the emptying of a caseous gland into a bronchus, or from sputum or blood aspirated from a quiescent or active pulmonary focus. In this way tubercle bacilli are deposited in the finer branches of the bronchial tree over a relatively wide area.

Their presence excites an immediate inflammatory response within the alveoli, resulting in the formation of a pneumonic exudate, and thus parts of a lobe, the whole lobe, or sometimes the entire lung may become consolidated.

These acute tuberculous consolidations are classified into two groups—lobar, or caseous pneumonia; and lobular, or tuberculous bronchopneumonia. Bronchopneumonic areas may rapidly coalesce and form lobar consolidations of the lungs.

The lobar form is rare, but the bronchopneumonic type is comparatively frequent.

Acute tuberculous pneumonia (*caseous pneumonia, pneumonic phthisis*) is rarely, if ever, encountered in patients suffering with active chronic pulmonary tuberculosis, nor is it met with in infants or young children. Usually it attacks adults in apparently excellent health. There are no criteria to differentiate its early stages from ordinary croupous pneumonia. It is a type of pulmonary tuberculosis seen in general practice, not in health resorts or sanatoria for the tuberculous.

Morbid Anatomy.—Regarding the location of the pneumonia in the lung statistics are meager and, therefore, unreliable, but the consensus of opinion indicates that the upper lobe is most frequently involved. During the first week or ten days its gross appearance cannot be differentiated from ordinary lobar pneumonia in the stage of red hepatization. Soon after, however, caseation (an essential characteristic of tuberculosis) develops and the consolidated portion on section shows a smooth, dry surface of yellowish or grayish-white color, and of the consistency of cheese. At times there is a marbled appearance due to strands of hyperemic lung tissue coursing between large areas of caseation. The adjoining lung tissue not actually involved in the pneumonia has a gelatinous appearance. Although extensive portions may be uniformly caseous, yet necrosis and cavity formation may occur at the same time in other parts of the affected lung. A group of several small, ragged-walled cavities may quickly break down to form one large irregular excavation. Occasionally, with great rapidity, a whole lung may be thus completely destroyed.

The pleura overlying the morbid process is inflamed, its surface rendered lusterless by a deposit of fibrin. Usually an old tuberculous focus, possibly containing a small cavity, is found at the apex of the lung.

During the period of acute inflammation there is little or no evidence of the formation of fibrous tissue, but if the patient survive the pneumonia, extensive bands of fibrous tissue may eventually be produced.

Symptoms.—The onset of caseous pneumonia simulates in every way ordinary lobar pneumonia. There is the sudden chill and high fever, increased respiratory rate, pleural pain, cough and rusty colored sputum. Unlike croupous pneumonia, however, a small hemoptysis may occur; the high fever usually shows daily remissions of a degree and a half or more; and cyanosis is not often observed. The pneumonia runs the usual course, but at the time of the expected crisis none occurs. Instead, the fever continues high, with greater daily remissions, and the expectoration becomes abundant, purulent, and at times greenish in color. There is rapid emaciation, profuse sweating, and, in the majority of cases, ultimate death. Those who weather the storm gradually pass into the chronic stages of pulmonary tuberculosis.

The failure of resolution suggests the tuberculous nature of the disease, and the examination of the sputum at this time usually reveals large numbers of tubercle bacilli. Osler reports a case where tubercle bacilli were found four days after the initial symptoms of the pneumonia.

Physical signs in the early stages are similar to those of lobar pneumonia, namely, limitation of motion of the affected side; dulness on percussion over the consolidated area; bronchial breathing, bronchophony and whispered pectoriloquy, and showers of fine râles. The later stages of caseous pneumonia differ from lobar pneumonia in that with the appearance of coarse, moist râles there is no crisis in the fever, and instead of resolution there are the signs of softening and breaking down of lung tissue.

If the patient survive the period of acute inflammation, the pneumonic exudate may be largely absorbed or replaced by fibrous tissue, and further necrosis and cavitation is held in check by this scar tissue. The physical signs remaining are those of consolidation (unresolved pneumonia) and probably of cavitation.

Death has been known to occur as early as the sixth day (Tendeloo), but usually the disease runs from a few weeks to several months, while a few of those stricken eventually become chronic cases of pulmonary tuberculosis.

The following features may help to differentiate caseous pneumonia from ordinary lobar pneumonia: the fever, instead of being continuously high, shows daily remissions of a degree and a half or more; there is no crisis upon the appearance of coarse bubbling râles; hemoptysis of a frank nature may occur; the leukocyte count is not increased; there is early evidence of cavity formation. Later the rapid emaciation, septic temperature, profuse sweating, and copious expectoration confirm the earlier diagnosis. The sputum shows large numbers of tubercle bacilli.

Acute Tuberculous Bronchopneumonia (*Phthisis Florida, "Galloping Consumption"*).—Acute tuberculous bronchopneumonia is the more common of the two types of acute tuberculosis. It is the chief cause of death in pulmonary tuberculosis of infants and young children. In adults it sometimes attacks individuals in apparent good health, but more often it occurs during the course of chronic pulmonary tuberculosis by the aspiration of bacilli-laden sputum or blood (from an hemoptysis) into the healthy portions of the lung. It may be the terminal event of a chronic phthisis.

In negroes and other races that have not obtained a relative immunity toward tuberculosis by centuries of contact with it, tuberculous bronchopneumonia is the predominating form of the disease in those stricken. The bacillus falls on fertile soil.

Morbid Anatomy.—In its first stages tuberculous bronchopneumonia simulates non-tuberculous pneumonia both as to its appearance and distribution. With the advent of caseation there are seen small whitish areas grouped around a bronchus. These grape-like clusters show ill-defined yellowish borders which fuse imperceptibly with the surrounding tissue. They spread and coalesce with similar areas, resulting in an involvement of considerable lung tissue. With softening of the mass cavities may be found. During the stages of exudation and caseation there is little or no fibrous tissue formation, but later on there may be an abundance of this tissue produced. In adults an old tuberculous focus is usually found at the summit of the lung. In children the disease is often bilateral in its distribution in

the lung, and the tracheobronchial lymph-glands are practically always enlarged and caseous.

Symptoms.—At first the symptoms may be those of acute bronchitis with cough and scanty expectoration. Later the fever is high, with marked daily remissions. The pulse rate is increased, the respirations quickened, sweating is common, and emaciation rapid. The cough becomes excessive and the sputum abundant and purulent. Cyanosis is common and may be especially marked in advanced cases of pulmonary tuberculosis that develop a bronchopneumonia following hemorrhage. On the contrary, in other cases the skin may be pale and hot, the cheeks flushed, the eyes bright; there is dyspnea, hectic fever, rapid emaciation, sweating, and death.

Physical signs are variable. At first there may be only the sonorous sounds of a diffuse bronchitis. Later the signs of consolidation gradually make their appearance. There may be more than one manifest pneumonic area in a lobe, so that small patches of bronchial breathing are heard. In time these may coalesce to form a large consolidation. Often with amazing rapidity the signs of cavity appear—cavernous breathing and gurgling râles.

The pneumonic areas are usually found in the upper portion of the lungs in those cases uncomplicated by pre-existing pulmonary tuberculosis. When chronic phthisis is present the lower portion of the lung or the central region of the opposite sound lung are common sites of bronchogenic pneumonic invasion. In the latter case the signs of consolidation are found in the axilla and under the pectoral fold.

The prognosis of acute tuberculous bronchopneumonia is poor. Those who survive the acute stages gradually pass into the chronic state and continue so for many months or even years. Occasionally a child or young adult with extensive tuberculous bronchopneumonia will show a remarkable recovery from the acute symptoms with a return to apparent health, but with a persistence of the physical signs of consolidation accompanied by moist râles. These individuals live in jeopardy of a profuse hemoptysis, or a recrudescence of activity with further extension of the lesions and ultimate death.

The diagnosis of tuberculous bronchopneumonia rests upon the protracted course of the acute symptoms: rapid wasting, profuse sweating, early signs of cavity formation, and the finding of tubercle bacilli in the sputum. In infants and young children with extensive bronchitis rapid emaciation is of great significance as pointing toward a tuberculous origin of their disease.

Non-tuberculous pneumonia occurring during the course of active pulmonary tuberculosis is rare. Hence in patients known to have pulmonary tuberculosis the sudden onset of the symptoms and signs of fresh consolidation point to a pneumonic spread of their tuberculosis rather than a non-tuberculous infection.

Edward N. Packard.

Chronic Ulcerative Tuberculosis of the Lungs

Definition.—This form of tuberculosis is characterized by the formation of areas of softening and ulceration in the pulmonary tissue. These areas eventually lead to the formation of cavities.

Incidence.—Chronic ulcerative tuberculosis of the lungs is by far the commonest form of pulmonary tuberculosis. It is essentially a disease of

young adult life, most cases occurring between the ages of twenty and forty. It is less commonly encountered in children under fifteen years of age. Season and climate appear to have little effect upon the incidence of the disease.

Pulmonary tuberculosis occurs more frequently in the male than in the female, probably because the male leads a more strenuous life and bears a greater responsibility in the struggle for existence. The disease is more common in cities than in the country. One of the most important factors in the incidence of tuberculosis is the character of living conditions. In the crowded tenement sections of our large cities the death rate for tuberculosis is invariably higher. As living conditions improve the death rate falls. Certain occupations also predispose to tuberculosis, more particularly those in which the worker is exposed to dust from marble, stone, plaster, etc. Occupations that necessitate close confinement within doors or unsanitary conditions of living are also important factors in the etiology of the disease.

Morbid Anatomy.—The lungs receive infection either by the inhalation of *tubercle bacilli* or from the blood; if through inhalation, infection may be *primary*, so far as the body is concerned; if from the blood, it is always *secondary* and comes from an extrapulmonary focus. If infection is from without by the air passages, it is likely to begin as an isolated tubercle; if from the blood, either as an isolated or disseminated (including miliary) tubercle. In either case the tubercle develops first in the lymphatic domain. At birth the lymphatics of the lung are free from foreign material, equipped with relatively little aggregated lymphoid tissue, and function quite actively. With increasing age there is an increased amount of intrapulmonary lymphoid tissue situated along the lymphatics wherever bronchi, bronchioles, arteries, and veins bifurcate. At the same time more and more inhaled particulate matter is deposited throughout the lymphatics, while in response to the irritation of inhaled dust, soot, etc., the intrapulmonary lymphoid tissue proliferates. All this serves to make lymphatic drainage in the lungs less active and easy in the adult than in the young. The result is that particles coming to the lung are less likely to be carried to the lymph-nodes of the hilum as age advances.

Every type of pulmonary tuberculosis can exist at every age. Infants, children, and adults—all may suffer from acute or chronic tuberculosis; sclerotic, pneumonic, or miliary tuberculosis; tuberculosis with cavity, pleurisy with effusion, and pneumothorax; tuberculosis at the periphery or at the root. But, by and large, there is a form that is rather typical of early life and a different form that is almost characteristic of adult life. In *children* pulmonary tuberculosis is prone to manifest itself as an affection most prominent at the root, with later evidences scattered through the lungs. In *adults* it is the rule for the disease to begin out in the lung and, in the great preponderance of cases toward the apex of the lungs, and to spread downward and mesial as the infection progresses. A freer and more active lymphatic drainage probably explains the marked tendency for the infection to accrue at the hilum in childhood, just as a comparatively impervious lymphatic system favors intrapulmonary fixation of bacilli in adults, but quite likely there is also another factor at work; this is the operation of the allergy acquired from antecedent infection. As we have seen, most adults, presumptively infected, are presumptively allergic. If, then, the reinfecting bacilli enter the lung either from the air passages

or the blood, they tend to be fixed there by the prompt allergic response. On the other hand, bacilli coming to the child's lung are more likely to fall on virgin soil, arouse no allergic reaction at first, and find lymphatic transportation to the lymph-nodes at the hilum relatively easy.

The allergic state has other effects that are as deep seated and far reaching as that contributing to the intrapulmonary fixation of bacilli. It modifies the character of the ensuing pathological processes. When relatively few or moderate numbers of the bacilli of a *primary* infection lodge at a given point they cause the slow development of a tubercle, which later becomes acute, as bacilli spread to various parts of the body and cause progressive tuberculosis. When comparable numbers of bacilli reinfect an organism they set up an acute inflammation, upon the subsidence of which a chronic and sclerosing tubercle develops at the point, as meanwhile few bacilli have spread from this focus. What has happened is a fixation and perhaps a destruction of bacilli in the reinfected animal. This destruction when not total leaves comparatively few survivors, which then cause relatively mild fibrotic changes.

All our knowledge favors some such conception of the origin in man of what is called *chronic ulcerative phthisis*. When such lesions first become active clinically they are usually discrete, rather indurative, fibrocaseous processes at the summit of the lung. The history of these changes before the appearance of symptoms is quite important to our understanding of them. Unfortunately, our direct and detailed knowledge is relatively slight; yet we are fairly certain of several general features of the origin and development.

First, in a vast number of instances the tubercle from which this phthisis developed has existed for a long time—months and years.

Second, in many cases this antecedent process has throughout a long period maintained a state of clinical quiescence because fibrosis has kept well ahead of necrosis.

Third, some contributory etiological factor, such as intercurrent disease, overstrain, etc., has operated to disturb this favorable relation, so that necrosis encroaches on fibrosis and becomes predominant.

Further, when the original process formed, it was doubtless initiated by relatively few bacilli which, lodging in allergic soil, set up a local inflammation so slight as to be inappreciable, and which produced a more benign tubercle than if the allergy had not existed. Or if the original infection was primary (as concerns the body) the number of bacilli might have been so small that only a very indolent and fibrotic early development of the tubercle was possible.

At any rate, because of adverse environmental conditions, a time may come when the bacilli concerned take on new capacities of multiplication, and the destructive processes, such as represented by caseation, acquire a new vigor. The old fibrous envelope then is invaded, a new zone of congestion surrounds the tubercle, bacilli are perhaps carried outside to set up fresh tubercles, there is unwonted absorption of intoxicating materials, and clinical symptoms develop.

As the process slowly spreads and approaches bronchioles or bronchi, its outriding zone of congestion arouses in these a local catarrh. As it abuts against a blood-vessel or a bronchiole it begins to involve these organically. It weakens the walls of blood-vessels until they finally give way and cause

hemoptysis; it erodes the bronchiolar wall and thus establishes ulceration. Perhaps a few bacilli are carried out of a capsule that has not yet actually been broken through by the caseating center, and appear in the sputum. As this interior focus of necrosis comes to communicate openly with the air passage, more of the tubercle's contents are discharged with the sputum, which may then contain numerous bacilli, pus, bits of caseating tissue, and fragments of more resistant pulmonary tissue (elastic tissue) that have been caught in the necrotizing process.

Undoubtedly a fibrocaseous, infiltrating, apical tubercle is capable of causing clinically active disease before actual ulceration has occurred; for, as has been mentioned, its influence through allergic congestion may extend beyond its borders, involve air passages in local catarrh, and thus give rise to cough, expectoration, etc.; while less competent fibrosis with enhanced necrosis, or the development of a fresh tubercle nearby, may permit absorption of materials that intoxicate and produce constitutional symptoms. But it is when such a tubercle ulcerates that the condition becomes immeasurably more dangerous.

For we now have in open communication with the air passages and in indirect communication with the digestive tract as well a necrotic lesion sown with *tubercle bacilli*, and opportunities for the spreading of the infection are enormously enhanced. It is hardly necessary to mention the dangers of laryngeal or enteric tuberculosis—two of the most serious complications of pulmonary disease—which are now added to that of widespread involvement of the lung itself and of the opposite lung besides. If the process continues, the ulcerating focus may become a cavity which gradually extends its boundaries, and other foci may spring up in the same lobe as sputum-borne bacilli are carried through the mucosa of the air passages. By successive reinfection of this nature the entire lobe may be involved.

A person with a chronic ulcerating focus, with or without cavity, is highly allergic. Therefore, whenever new reinfections from the parent focus take place there will be a prompt inflammatory response. If the bacilli of any particular reinfection are few, the inflammation will be too slight to be noticeable, and will pass off without clinical symptoms; but if the numbers of bacilli brought to one point are large enough they will soon set up a local congestion or pneumonia, and the patient, who has for a time suffered from low-grade symptoms, manifest acute symptoms, the temperature will become more elevated and prostration more pronounced. The course of the ordinary case of chronic ulcerative pulmonary tuberculosis is punctuated with variable oscillations, from chronicity to acuteness and *vice versa*, with numerous periods of comparative freedom from symptoms in between. Many of the more acute phases are due to an increased activity of bacilli in preexisting tubercles which augments caseation (or *softening*, as we say clinically) and greater absorption of focal poisons, but many are also the expression of an acute congestion or pneumonia set up as described above.

A patient who for a long time has been in a rather indifferent and chronic condition may suddenly become very ill, and a week or two later a wide area of the lung, usually lower down than the old focus, will present signs of pneumonia. This condition is so definite when it occurs that it is recognized as a more or less special phase of pulmonary tuberculosis and is designated *acute tuberculous pneumonia*. Pathologically, it is always a

secondary process. It occurs most frequently when the contents of an upper lobe focus are discharged and aspirated in large quantity, to settle within a comparatively small space below. Besides appearing abruptly in a person with known active pulmonary tuberculosis, this condition not infrequently ushers in the disease in patients who have not been manifestly ill before. Nevertheless, close questioning may show that a large proportion of these apparently normal individuals have not enjoyed the best of health for some time previous to the acute onset of disease, and it is highly probable that most of them have suffered unconsciously from a mild chronic tuberculosis due to the tubercle that has suddenly broken.

This bringing together by aspiration of much bacilli-containing focal material at one point is most favorable to the development of the inflammation of tuberculosis. There is an abrupt exudation throughout a large territory —perhaps several inches in diameter. It is, however, important that the bacilli need not be distributed throughout the pneumonic patch; indeed, they usually are not, but are at the center, whence their allergic influence extends in all directions for several inches beyond their site. This pneumonic zone, itself not penetrated by *tubercle bacilli*, is what some authors have called the *collateral inflammation of tuberculosis*. Others have attributed it to "secondary micro-organisms," such as pneumococci, streptococci, etc.—a thoroughly unnecessary and undoubtedly erroneous assumption.

If this prompt inflammatory reaction succeeds in limiting the bacilli to the center, it gradually subsides, clearing up from the periphery inward. Clinically, there is evident a fairly rapid and satisfactory shrinking of the involved patch, but at the center a residuum which represents the site of the bacilli themselves is likely to persist for a long time. Fixed by the rapid allergic response, and thus kept from spreading throughout the whole lung and doing greater damage, the surviving bacilli then go on and reproduce the cycle of nodular tuberculosis already described, with all its possibilities of proliferation, necrosis, and repair.

Thus chronic ulcerative phthisis may continue to spread throughout a lung from above downward and from one lung to the other. Of course, with the development of new ulcerating foci the possibilities of bronchogenic dissemination become greater and greater. Scattered throughout the lung may be seen nodular tubercles of every size and in every stage of development. The involved areas appear smaller in size at the bottom than at the top of the lung, and there is a great diversity and jumble of effects resulting from the proliferation, exudation, necrosis, and fibrosis of varying intensity at different times and in many different locations. Besides intrapulmonary effects, there arise the evidences of infection as it involves the periphery of the lung: a pleura thickened and scarred in patches that are most prominent at the summit of the lung where the process was chronic for the longest time; adhesions of every shape, size, and density running over to the chest wall; perhaps, more toward the base, a densely thickened and, maybe, partially necrotic pleura that once poured out an effusion, serous or seropurulent, into the thoracic cavity and later became organized. Or, perhaps, when the chest is opened, the lung may lie collapsed against the vertebral gutter, and a rent may be discovered in the pleura where it has become thinned out over a subpleural cavity, and by giving way has produced pneumothorax.

Section of the lung of an individual who has died after years of advanc-

ing chronic ulcerative phthisis usually discloses more or less excavation of the upper lobe, which is perhaps a mere fibrous shell bounding a cavity traversed by distorted cords, the remnants of blood-vessels; and below this, extensive patches of caseation surrounded by fibrous tissue, with a deep red zone of inflammation radiating from it, and other tubercles of variable appearance scattered throughout the lung. Evidences of healing, such as completely fibrous tubercles and calcified nodules, may also be seen; and besides, the non-specific overeffects of a tubercle; weakened bronchi that have bellied out into bronchiectases; patches of non-tuberculous atelectasis that have been shut off from air passages; thrombosed blood-vessels that have been pinched in their course by encroaching foci; large blebs of thinned-out air vesicles that have assumed the function of obliterated alveoli; and a more bizarre appearance of the whole surface caused by the piebald blacks, grays, and greens of inhaled particles laid down throughout a lifetime along the rich and complicated basketry of lymphatics which embraces everywhere the bronchial and vascular trees and spreads out through the entire pleura.

ALLEN K. KRAUSE.

THE SYMPTOMS OF PULMONARY TUBERCULOSIS

The symptoms of pulmonary tuberculosis are extraordinarily variable during the earliest stages, and may in some instances be discovered only by careful questioning. A so-called mild indisposition or a slight transient cold may mark the onset of this frequently insidious disease. As it progresses the symptoms, which at first may be only general, gradually become more and more localized. The malaise, vesperal fever, slight tachycardia, and loss of weight and strength are soon accompanied by coughing, expectoration, and frequently by pleurisy and hemoptysis. For months after onset the periods of illness are often comparatively brief and are associated with attacks of bronchitis, following rhinitis or coryza. Physical examination of the lungs during this period may reveal no lesions or only those of doubtful etiology. After this prodromal period is passed, however, and throughout the moderately advanced stage the symptoms become more characteristic. Fortunately, they usually manifest themselves early; and because antituberculosis propaganda has aroused the public and acquainted it with the early manifestations, patients often seek medical advice as soon as any suspicious symptoms appear. Although the diagnostic significance of symptoms is quite widely recognized, the fact that the type of treatment, the amount of activity permissible, and the prognosis depend upon the number and character of these manifestations is not so generally appreciated.

The physical signs, which are also important, are not always closely related to the symptoms. They may develop long before any subjective changes are noticed, and their severity frequently does not run parallel to that of the symptoms. While *tubercle bacilli* may be present in the sputum when there is no other evidence of pulmonary tuberculosis, it is more common for them to be absent until several months after the onset of the disease.

Although pulmonary tuberculosis has from time immemorial been considered to pass through three stages characterized by infiltration, consolidation, and the formation of cavities, it seems more practical now to classify cases according to the extent and severity of the lesions in the lungs as

revealed by physical and *x*-ray examinations, but since classification of cases into incipient, moderately advanced, and advanced or far advanced groups is purely arbitrary, it seems more satisfactory to discuss each symptom separately rather than to attempt to outline the syndrome characteristic of each stage.

Cough and Expectoration.—Cough, productive (with sputum) or dry, is the most common and often the earliest and most persistent symptom. It may escape attention for months, be attributed to smoking, occur only after deep or rapid breathing (*e. g.*, laughing, rapid and loud talking, singing, etc.), and may have no connection with the number or location of the râles. The type which follows coryza is usually first considered a symptom of simple bronchitis which may disappear after a slight change of climate or the advent of warm weather, only to recur. The cough is rarely absent. It depends more upon the amount and quality of sputum and probably the location of the lesion (*i. e.*, its proximity to the bronchial wall and the degree of involvement of the pulmonary nervous tissue) than upon the severity of the disease. Chilling or lying upon the affected side at times produces or aggravates it. Because sputum collects in the bronchi during the night coughing is usually most frequent in the morning, but it may occur continuously throughout the day, with exacerbations after meals and on lying down. The cough usually assumes a paroxysmal and emetic character only in the more advanced stages, when much of the resilience of the lung is lost and the muscles used in vomiting are employed to produce additional pressure upon the lungs when secretions need to be removed.

Severe coughing is frequently the cause of involuntary passage of urine (especially in women), pain or soreness in the chest and abdomen, hernia, displacement of the uterus, abortion, physical exhaustion, profuse sweating, cyanosis, tachycardia, dyspnea, aspiration of sputum into normal areas, pneumothorax, and subcutaneous emphysema.

Many patients are able after practice to suppress the cough in large part and to raise the sputum by "clearing the throat." Expectoration may be almost the first symptom and may persist throughout the remainder of life. The amount of sputum often bears no relation to the severity of physical or *x*-ray signs. It may be so great that the patient expectorates day and night (true bronchorrhea) and is threatened with exhaustion.

Hemoptysis occurs in about 50 per cent. of patients, somewhat less often in women than in men. It is most common during the years of greatest activity, is rare before puberty, much less common in acute than in chronic pulmonary tuberculosis, and seems to be independent of heredity and, indeed, of discoverable abnormal physical signs in many early cases. Such bleeding usually takes place more than once and the sputum is often stained with blood for one or two days after the hemorrhage. Nocturnal hemoptysis is not uncommon. Pink or rusty streaks in the sputum may be caused by blood which has seeped through the bronchial wall (diapedesis). While not infrequently a sign of activity of the pathological process, its presence may not be of serious import. The blood is usually derived from the pulmonary artery, rarely from either the pulmonary vein or bronchial artery. Its color is not an index of its origin. Fatal hemoptysis most often follows rupture of a vessel or of an aneurysm on one of the middle-sized branches of the pulmonary artery, usually in the wall of a small cavity, rarely in a bronchus, and most often in the lower part of the upper lobes.

The blood, which varies in quantity from the slightest trace to several liters (usually less than 15 c.c.), may be coughed up in small amounts every few minutes, or gush from the mouth or nose. Much may be swallowed. Fatal hemorrhage into a large pulmonary cavity can occur without hemoptysis. Hemoptysis is severe and profuse in 1 patient in 20. *Tubercle bacilli* may be present in the blood, which is often clotted just before the bleeding ceases.

Etiology.—Hemoptysis has been attributed to many causes. When ulcerative processes spread more rapidly than endarteritis, or when strain weakens or ruptures the wall of a diseased vessel, hemoptysis may result. Lung stones may produce slight bleeding for long periods, which ceases when the stone is expectorated. Although sudden *overexertion* has long been considered a cause of hemoptysis, blood appears in the sputum of only one-fifth of the patients who expose themselves to such undue strain. Overexertion may, however, so weaken the wall of a diseased vessel that it is unable to withstand the rapid changes of pulmonary blood-pressure which take place in the early morning, or follow acceleration of the pulmonary circulation after excitement, coughing, or exercise which produces dyspnea.

Unsuccessful attempts have been made to relate the occurrence of hemoptysis to barometric or seasonal changes. Heliotherapy, pulmonary infections with the *pneumococcus* or *Streptococcus hemolyticus*, and inhalation of irritant gases (ether) have been thought to play an etiological rôle. The hemoptysis which sometimes just precedes menstruation may be severe.

In 589 fatal cases of pulmonary tuberculosis hemoptysis was observed in 60 per cent. and was soon followed by death in 7 per cent. In 24 fatal cases the cause of severe bleeding seemed to be: lobar pneumonia 3, bronchopneumonia 3, acute congestion 1, hemorrhagic infarct 3, rupture of a blood-vessel 3, unknown 11. In 214 patients hemoptysis was associated with an acute lesion in 55 per cent., softening in 37.4 per cent., heart disease in 3.2 per cent., and menstruation, infarct, and rupture of a blood-vessel in 1.4 per cent. each (Joseph Walsh). It usually proves fatal because of asphyxiation in chronic fibroid cases and because of syncope or exhaustion in other types. In a large proportion of cases hemoptysis is accidental and affects the immediate course of the disease but little. Even when slight, however, it may precede severe or fatal bleeding. If blood is not expectorated for forty-eight hours recurrence is less likely.

Sequelæ.—*Slight fever* due to absorption of the disintegrated blood often continues for a few days. *Profound prostration* may succeed even slight hemoptysis.

At the Trudeau Sanatorium observation of 1810 patients seemed to demonstrate that hemoptysis exerted a more deleterious influence upon the course of the disease in men than in women. The death rate among 1276 discharged patients who had had this symptom was slightly higher for the men. Hemoptysis appears to have no after-effects in women.

Pain.—*Thoracic pain*, which sooner or later attacks a large majority of patients, has been attributed to pleurisy, pneumothorax, contraction of old cavities, pulmonary congestion, traction on pleural adhesions or on the heart, stretching of an inflamed parietal pleura, advancing or active pulmonary disease, pressure from enlarged glands, neuralgia, neuritis, extension of inflammation to the intercostal nerves, myositis, and localized fatigue of the muscles used in breathing or coughing. It may be either slight

and felt only during a full inspiration and expiration, or sharp and lancinating, and produce dyspnea, sweating, and great prostration. When slight the pain may be associated with a short, dry, hacking cough and fever. Sudden cessation suggests accumulation of pleural fluid. Diaphragmatic pleurisy causes referred pain along the trapezius ridge when the central portion is affected; over the lower chest and abdomen when the outer 2 to 3 inches are involved.

Pain may precede an hemoptysis and disappear after the hemorrhage. Cutaneous hyperesthesia, attributed by some to an acute extension of the disease, may be so pronounced that the clothes cause discomfort, or may be discovered only during percussion. Fleeting pains are not uncommon. In a few cases the pain may suggest angina and radiate down the arm. Severe pain may develop just before the eruption of herpes zoster or mark the onset of pneumothorax before the physical signs are demonstrable.

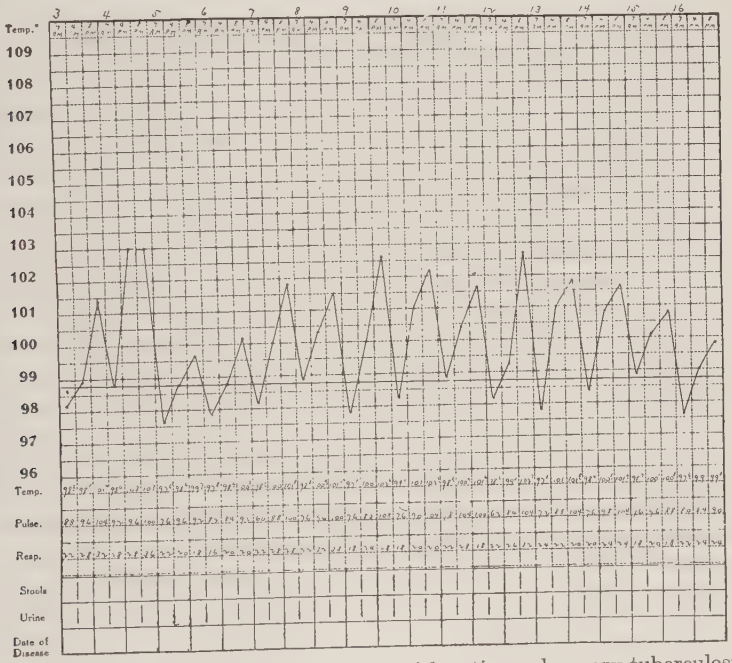

Fig. 4.—Temperature chart of a patient with active pulmonary tuberculosis.

Fever.—The temperature curve of a tuberculous patient remains almost unchanged as long as fever persists. The level is characteristically often subnormal in the morning and above normal in the afternoon. The successive exacerbations are separated by intervals of days or weeks when the temperature is normal or slightly elevated. Fever may precede all other symptoms and is present sooner or later in most patients, although when a properly regulated régime is established in the very early stages the temperature may remain normal.

Etiology.—The poison produced by *tubercle bacilli* has long been considered the cause of fever, but Krause has shown that absorption of disintegrating tissue probably plays the most important etiological rôle. Tuberculin causes a focal congestion which facilitates local absorption. The

form of the daily temperature curve is explained by rest at night and morning exertion (cough, toilet). Whatever facilitates absorption may produce high fever; whatever limits it usually abolishes fever even when the disease is progressing slowly and emaciation becomes more marked. Occlusion of a bronchus or the outlet of a cavity may, by permitting absorption, cause fever. Lack of free water, which may carry heat from the tissues to the surface of the body, promotes fever. Although mixed infection is said to cause high remittent fever, little evidence of it has been obtained. The fever of tuberculosis is frequently quite unassociated with constitutional disturbances.

Types of Fever.—In acute tuberculosis and in acute exacerbations of the chronic form fever is often marked. Although it sometimes simulates that of typhoid, it more often is continuously high and slightly remittent. In the rare instances when it is more or less regularly intermittent it suggests malaria.

Every known type of fever is associated with *chronic tuberculosis*, but the most characteristic temperature curve begins at normal or slightly below in the morning, rises to between 99.5° and 100° F. between noon and 9 P. M. (usually from 3 to 5 P. M.), maintains this level for one to three or more hours, and then falls gradually until the lowest level is reached between 2 and 4 A. M. Exacerbations of fever, when the temperature rises to 101° or 103° F., occur at varying intervals and mark extension of the disease. They usually persist for about fourteen days, the period required for the formation of antibodies. Between such attacks (one to eight weeks) the temperature may be normal. There is frequently a fall in temperature when excavation of a cavity ceases. In pulmonary tuberculosis the fever usually increases by steps, and a sudden marked rise of temperature is practically always due to the onset of some complication. The nervous instability so common in pulmonary tuberculosis leads to acceleration of the circulation by slight mental or physical stimuli that would normally pass unobserved, and coupled with the allergic state explains in large measure the variations in temperature.

While the disease may slowly progress without fever in advanced cases, persistent elevation of temperature is the best indication of activity. It may, however, provide little evidence of the extent of the lesions. Destruction of tissue is often associated with high remittent or sometimes with intermittent fever. The temperature may return to normal before the physical signs demonstrate the site of the new lesion. If hemoptysis causes any change in the temperature, the fever usually rises and continues, but in a few cases it may subside. Great emphasis is now laid upon the fact that slight persistent elevations of temperature, which occur during treatment for pulmonary tuberculosis, are probably indicative of the onset of activity in the lesions. In a few instances slight fever is apparently due to absorption of material from an old cavity. A subnormal temperature or very irregular variations in the curve which is at times normal for a day or two are characteristic of intestinal tuberculosis. The reverse type of temperature is unusual. Slight fever from one to fourteen days before menstruation has been noted in between 50 and 60 per cent. of patients. A slight postprandial rise is common. In neurotic patients "thermometer fever" may occur. At the Trudeau Sanatorium temperatures as low as 91° F. or as high as 106° F. and a diurnal range of 10° F. have been recorded.

The oral temperature when properly taken (mouth closed for fifteen minutes before insertion of the thermometer) never fails to reveal the delicate changes which order the life of the patient. During the first two or three days of treatment it is wise to take the temperature every two hours in order to determine the time of the highest temperature. The normal range of oral temperature is between 97° and 99° F. The rectal temperature is about 1 degree higher for low or normal temperatures, but above 102° F. is much nearer that of the mouth, and ultimately becomes almost the same. Exercise, walking or even standing, markedly affects rectal temperature.

Changes in Weight.—Next to the temperature variations, changes in weight are the most important index of the progress of the disease. *Loss of weight*, which occurs in almost every patient, affects all organs of the body except the liver, which may undergo a fatty change, and possibly the bones. It is due not only to lack of appetite but also to inability to assimilate ingested food. The few patients with slowly advancing tuberculosis who lose no weight have probably a fair general, but poor local, resistance. The digestive ferments are said to be decreased. While not necessarily dependent upon fever, the loss of weight often lessens as the temperature falls.

Exercise, especially forced, accelerates the circulation, increases absorption of poisons at the focus in certain stages, interferes with cell assimilation, and thus causes loss of weight. When this amounts to 30 or 40 per cent. of the normal weight it is always serious. Emaciation may be marked by edema or effusion. A loss of 5 or 6 pounds a week for several weeks is not unusual. One patient who weighed 271 pounds is reported to have lost 130 pounds.

The fact that *gain in weight* has been considered a very important sign of progress has led to much harmful overeating. Patients who take a well-balanced diet gain more quickly than those who eat chiefly meat. The weight usually increases after fever decreases, but there may be gain even with fever when the routine is properly ordered. Change of environment often stimulates temporary gain even in advanced stages. Cold has a similar effect, and may somewhat exaggerate the usual yearly variations of body weight. Great dryness has not this tendency. While under treatment men lose more and gain less than women. Weight gained during exercise is more permanent than that gained during rest as the result of taking large quantities of milk and eggs. The optimum weight is the normal plus 10 pounds.

Metabolism.—Without fever the basal metabolism of tuberculous patients is normal except before or during menstruation. In 10 cases it varied from minus 3 to plus 10 per cent., but when the temperature was 104° F. it rose 30 per cent. The basal heat production is less than normal. Emaciation may be accompanied by a reduction in the rate of metabolism which more than compensates for the increase caused by the disease. Limited data show that the amount of protein destroyed is not large. The specific dynamic action of ingested protein is about normal. McCann believes that forced feeding is unnecessary and probably harmful, and advocates limitation of the protein intake when the disease is active in order to put the lung at rest. Hill and Campbell found the heat production of clothed adults to be increased 40 to 50 per cent. by an outdoor life; of partly nude children, 60 to 90 per cent., and of clothed children in a cold wind on a cloudy day, 200 per cent.

Loss of strength may be the first or most noticeable symptom, is at times out of proportion to the physical or even *x*-ray findings, and in the beginning is characterized more by lack of endurance than by inability to execute a single act. In the late stages of the disease the patient must often remain perfectly quiet. The fact that strength at times returns very slowly has been attributed by some physicians to lack of certain internal secretions.

Night-sweats.—So-called night-sweats, which may often occur during sleep at any time, are rare in the early stages of tuberculosis, and since hygiene has improved are not common even in advanced cases. They may be slight and affect only the head, chest, or legs, or so general and severe as to soak the night clothes and at times the mattress. They have been attributed to poisoning of the sweat, vasomotor, and heat centers, to vascular hypotension, to latitudinal fall of body temperature, and other causes.

Changes in the Blood.—The condition of the blood varies with the stage of the disease, the rapidity of its course, and the complications. The erythrocyte count is usually increased and the hemoglobin content above normal. The facial pallor in later stages which does not involve the lips and mucous membranes is caused probably by oligemia. The leukocyte count is usually normal or slightly low except when a cavity or some complication, such as intestinal tuberculosis, develops. There is often an increase in the percentage of mononuclear and lymphocytic cells, especially in favorable cases. The number of eosinophils is usually not increased and the blood-platelet count is normal. Of the polymorphonuclear cells normally 5 per cent. contain one nucleus; 35 per cent., two; 42 per cent., three; 17 per cent., four; and 2 per cent., five. The percentage of cells with one and two nuclei increases as the pulmonary tuberculosis advances. Sedimentation of the erythrocytes in citrated blood occurs much more rapidly than in health, and has been attributed to a decrease of the fibrinogen or globulin content of the blood.

Tubercle bacilli are carried by the blood, but in America they have rarely been demonstrated except in acute conditions, in the preagonal stage, and after death. Landouzy and others in France have, however, described a tuberculous bacillemia. *Tubercle bacilli* may be present in the blood more frequently in cases complicated by advanced intestinal tuberculosis. A few observers have found secondary organisms in the blood frequently in the more advanced cases. This is of little significance.

The Circulation.—*The Pulse.*—The increased frequency of the pulse, which is strikingly characteristic, may occur before the rise of temperature, and, consequently, be the first sign of extension of the disease. The rate usually varies between 88 and 120, most frequently from 90 to 100. It may be low for several weeks, while the temperature is 101° and 102° F. The pulse responds quickly to slight mental excitement or physical exercise. The cough or a visit from the physician may raise it 20 beats. The rate may be high for months after the temperature is normal. Real tachycardia is rare.

The Blood-pressure.—In favorable cases the blood-pressure is usually normal, but often in the advanced stages, especially when there are ulcerative lesions, the systolic pressure is low and the diastolic high. In general, however, pulmonary tuberculosis affects the blood-pressure less than any other wasting disease. The difference between the lying and standing pressure may be greater than normal.

The HEART often undergoes little change throughout the course of the disease. In the early stages there may be slight atrophy or hypertrophy and later dilatation, especially on the right side. Acute dilatation is uncommon. The second pulmonic sound is frequently accentuated. In chronic tuberculosis with cavity formation the heart may be markedly displaced to one side. This dislocation may be so sudden as to be noticed by the patient. In one case the heart was near the right scapula. Under such conditions murmurs due to pressure are common; they may be of the machinery-hall type (continuous with a systolic intensification). Cardiac distress and palpitation are unusual. A murmur is often heard under the outer third of the clavicle and is more common on the left side and in men. The lower extremities are frequently edematous in the terminal stages, when cyanosis may become most pronounced, particularly in the morning and also after exercise.

THE SKIN.—Because of better hygiene, changes take place in the skin less often now than formerly. Certain abnormalities do, however, occur, such as slight general or patchy pigmentation, at times limited to the face or trunk; a rare erythema, somewhat similar to the rash of scarlatina, more usually associated with high fever; purpura also rare; herpes labialis with gastric disorders or following tuberculin reactions; herpes zoster; and, very rarely, cutaneous tuberculosis. Flushing of one cheek and ear, or both cheeks (hectic flush), is common when the disease is advanced, and hyperesthesia of the skin is not unusual. The nails may be down-curved and in late stages the fingers clubbed (Hippocratic digits). Other changes are pits and ridges not peculiar to tuberculosis, and "watch-glass nails," which are as broad as long and equally curved in all directions. These are closely associated with amyloid degeneration of the internal organs.

ALIMENTARY SYSTEM.—Symptoms referable to the gastro-intestinal tract develop in nearly every patient and are of great importance in treatment. A red or blue line on the edges of the gums is common in more advanced cases, and pyorrhea, dental caries, and bleeding from spongy gums are frequent. The condition of the tongue varies directly with the condition of the patient. The stomatitis (thrush, etc.) which appears sometimes during the later stages is of grave prognostic import.

The digestion may be perfect, but when the disease is advanced and the patient weak it sooner or later becomes impaired, especially in alcoholics and those with a constitutionally weak digestion. This is, no doubt, largely the result of the increased consumption of food. The early dyspepsia often disappears as tuberculosis improves or grows worse. Hyperacidity may occur at the onset as well as later. Gastroptosis is also a symptom which may be of reflex origin and follow changes elsewhere in the tract. More or less pronounced meteorism is very common, and aërophagy may be present. Nausea is common at all stages and may be felt only in the morning or at any time after ingestion of food. It is not infrequently accompanied by vomiting. Much more often, however, the vomiting is due to purely mechanical causes, such as the violent coughing which frequently follows change of position at meal-times. The odor of the sputum may produce nausea and vomiting. Loss of appetite at the onset is often caused by a poorly regulated diet. When the body needs food most the stomach may crave it least. Many patients have a small, fickle appetite, but can and do

eat well. Others lose all desire for food as soon as they see or smell it or when the temperature rises. Lack of appetite is often due to the frequency of meals.

Constipation may be marked throughout in spite of extensive tuberculous intestinal ulceration. It is sometimes caused by inactivity. Diarrhea is unusual in the early stages, becomes more frequent later, and while in many instances it is temporary and due to indiscretion in eating (milk, raw eggs), chilling of the abdomen, or swallowing the sputum, is more often caused by tuberculous enteritis or colitis. These conditions are unusual in the minimal, common in moderately advanced. and very frequent in far advanced stages. The vast majority of all symptoms referable to the gastro-intestinal tract are due to intestinal tuberculosis. Evidences of this are found in between 60 and 80 per cent. or more of all tubercular autopsies. Since a reliable method of diagnosis has been obtained 5 per cent. of the patients admitted to the Trudeau Sanatorium have been known to have this complication.

Genito-urinary System.—Except for tuberculous complications (*e. g.*, tuberculous epididymitis, nephritis) few abnormalities are to be found in the genito-urinary tract. The urine is usually normal in early cases except for changes caused by fever, diet (polyuria), or complications (nephritis, diabetes). In late stages there is often a diazo-reaction, and albumin and, at times, casts are present. *Tubercle bacilli* may at this period appear in the urine when no tuberculous changes in the tract are demonstrable.

Menstruation may be normal throughout, or the flow decrease, become irregular, and cease as the disease advances. It recurs when improvement sets in. The onset may be postponed by infection at puberty. Menstruation is frequently preceded by a rise of blood-pressure, acceleration of the pulse, some retention of nitrogen, a rise in the basal metabolic rate, some elevation of temperature, and, more rarely, by more or less severe hemoptysis and some increase in râles.

Pregnancy can occur at any stage and may check tuberculosis until after parturition. A rapid advance in the progress of the disease then often takes place. Lactation is normal. The milk may contain *tubercle bacilli*.

The Nervous System.—The special affinity for nervous tissue which is attributed to tuberculous toxin is the cause of the psychical changes, neuroses, psychoses, and neuritides that occasionally develop. The wide-spread belief that pulmonary tuberculosis is curable, which has replaced the old view that it is incurable, may account for a decrease in such manifestations; but chronic invalidism often lays bare concealed characteristics. Weakness may also produce emotional changes or cause patients to act like children. The mental faculties are usually retained until death, and may become more acute than normal. Depression usually follows diagnosis for a while, but when all hope is lost the *spes phthisica* supervenes. Every patient is more or less neurasthenic at some time, and at the onset the nervous symptoms may mask tuberculosis. Hysteria is rare, aphonia not uncommon. Psychoses are rare. Melancholia or ideas of grandeur and importance may predominate. Suicidal tendencies develop occasionally.

The reflexes may be at times somewhat exaggerated. Neuritis, especially of the arm or leg, and neuralgia of the intercostal and sciatic nerves are common. Dilatation or contraction of one pupil and flushing of one side of the face are considered the result of pressure on the sympathetic

system by a retracted or thickened pleura. Myoidema, which is common in later stages, is probably caused by a functional nervous derangement of the muscles. Herpes zoster, due to changes in the posterior root ganglia, is not unusual and is not located according to the site of the pulmonary disease. It occurs chiefly between the ninth and twelfth thoracic segments, but also on the head and as low as the knee.

Sexual desire is increased, probably by the forced feeding, vigorous health, and lack of exercise.

LAWRASON BROWN.

THE DIAGNOSIS OF PULMONARY TUBERCULOSIS

The importance of early diagnosis cannot be overstated, since in the later stages alleviation, and not cure, is all that can be expected. Recognition of moderately advanced pulmonary tuberculosis is not difficult, but the early and in some cases the advanced disease is not easy to diagnose. It should be kept in mind that the onset is most frequently catarrhal in nature, and that when a cold or cough persists for more than two or three weeks thorough examinations for tuberculosis may save many months of suffering. To delay treatment until *tubercle bacilli* appear in the sputum may prevent recovery. Diagnosis depends upon certain factors, among the most important of which are the history of exposure during early life, employment in trades involving inhalation of hard dust, prolonged mental depression or any debilitating condition, and the development of symptoms and physical signs.

Symptoms are of great diagnostic importance because they lead to examination of the patient, and may appear before characteristic physical signs. The localizing symptoms (hemoptysis, pleurisy, cough, and expectoration) are much more significant than the constitutional (fever, rapid pulse, and loss of weight and strength). Spitting of a dram or more of blood or pleurisy with effusion should arouse suspicion of tuberculosis. If both are present, diagnosis may be certain. Pre-existing tuberculous lesions of the joints, adenitis, obstinate, persistent hoarseness, ischiorectal abscess or fistula, and persistence of symptoms after measles or whooping-cough suggest pulmonary tuberculosis.

Fever.—A persistent slight afternoon fever (temperature between 99.5° and 100° F.) may be the earliest and only symptom except undue fatigue. Disturbed sleep and a slight tendency to sweat may reveal a nocturnal fever. When the rise in temperature is so slight as to be detected only if the temperature is observed every two hours, possible infection of teeth, tonsils, and sinuses, and hyperthyroidism must be excluded. The rise of rectal temperature after excerise is not of much diagnostic value.

Cough, dry or productive, is the most frequent early symptom. It may be remittent and be mistaken for a symptom of the common cold. A summer cough is always suspicious.

Hemoptysis is rarely a primary symptom. Blood may be derived from the gums, from the nose, and from varicose veins on the posterior pharyngeal wall or on the base of the tongue, but practically never in the larynx. When more than an ounce is lost, it almost always comes from nose, lungs, or stomach. Epistaxis as well as spitting of blood takes place when the blood is derived from the nasal passages. Hemoptysis is usually followed by expectoration of bloody sputum for several days or by repeated hemoptysis.

Discoloration of sputum by food or drugs (wine, tobacco, prunes, tomatoes, licorice) may be mistaken for that due to blood. Blood mixed with mucus or pus is almost always from the lungs, large clots are usually from the stomach, but may be composed of pulmonary blood which has been swallowed. If the blood comes from below the larynx, such extrapulmonary disturbances as ulceration of the trachea, cardiac disease, especially mitral stenosis, aneurysm, purpura, hemophilia, leukemia, pernicious anemia, scurvy, certain infectious fevers, atheroma of the pulmonary vessels, and abscess of the liver involving the lung must be excluded.

Hemoptysis of true pulmonary origin is in 90 per cent. of cases due to pulmonary tuberculosis. In fact, the spitting of a dram or more of blood must be considered the result of tuberculosis until proved otherwise. Physical signs may be absent while *x*-rays reveal a deep-seated, fairly extensive process. *Tubercle bacilli* may be demonstrable in the blood only after concentration. Hemoptysis occurs more frequently in bronchiectasis than in tuberculosis, and is also a symptom of bronchitis (especially fibrinous), gangrene, abscess, asthma, emphysema, acute lobar pneumonia, infarct, embolism, anthrax, syphilis, actinomycosis, spirochetosis, amebiasis, parasitic diseases (echinococcus, distoma), tumors (carcinoma, sarcoma), trauma—in fact, almost any pulmonary disease.

Physical Signs.—The diagnostic value of physical signs has been greatly overrated, and it is now widely recognized that deep-seated and extensive lesions may not alter the physical signs, and that the disease is almost always more marked than the physical examination indicates. It is often necessary for such examinations to be repeated, for temporary changes are not significant.

It must not be forgotten, however, that physical signs indicative of typical pulmonary tuberculosis may be found in a vigorous individual who has never been aware of the disease.

Although many signs, such as myoidema, the gingival line, persistent pallor of the palate or larynx, abnormal changes in the pulse rate or in the blood-pressure on standing up, differences in the size of the pupils, increased axillary sweating, curved or cyanotic nails, flushing of one cheek, spasm or atrophy of chest muscles, and a decrease in the vital capacity are of secondary importance, they may be suggestive. Tuberculous adenitis or scars left from it, tuberculous laryngitis, or a tuberculous lesion in any part of the body are of much significance in diagnosis.

Percussion is difficult, confusing, and at times misleading. It reveals changes caused usually by disease of some standing, which are, possibly, located deep in the lung and approach the surface slowly. Percussion changes may be remarkably slight, even in advanced disease, because of compensatory emphysema which may produce hyperresonance. Mapping out the movement at the bases of the lungs and the resonant supraclavicular areas may be helpful.

Auscultation in early cases yields evidence of the greatest importance. When the auscultatory evidence is doubtful, repeated examinations should always be made.

Changes in the rhythm or pitch of expiration or inspiration, spluttering breathing suggestive of fine râles which cannot be heard (granular breathing), wavy breathing, and weakened or distant breathing are always suggestive if limited to a small area above the third rib and third vertebral spine.

The normal changes at the right apex must be kept in mind. The whisper should be auscultated over the entire chest, as it may early reveal a suspicious area.

The most important data obtained on physical examination are easily detected, *i. e.*, moderately coarse râles which in the early stages are frequently confined to an area above the third rib and third (dorsal) vertebral spine. These can often be detected only during a fairly rapid, rather full inspiration, or after a cough at or near the end of a fairly complete expiration. Failure to detect such râles depends solely upon ignorance of how to elicit them. Râles can develop in almost any intrapulmonary disease, but their limitation to and persistence at an apex is typical of tuberculosis. They may occur, but rarely do, in heart disease, influenza, streptococcus pneumonia, and a few other unusual conditions. Tuberculosis may produce râles in any part of the chest, even in the bases posteriorly. It is best to assume that moderately coarse râles above the third rib and third vertebral spine are tuberculous until proved otherwise, and that those elsewhere are non-tuberculous until their cause is determined.

Pseudorâles may be produced by hair, slipping of the bell of the stethoscope, swallowing, muscular contractions in neck and chest, joint, tendon, and bursa sounds, sternal sounds, abdominal sounds, and those due to atelectasis and separation of the pleuræ in the sinus (marginal râles).

The most trustworthy signs of cavity are a "cracked pot" or amphoric note, whispering bronchophony, tubular, amphoric, or cavernous breathing, and metallic, resonant, or gurgling râles.

x-Ray examination is valuable, but necessitates long study in doubtful cases. Physical signs usually provide a much more ready basis for diagnosis than do *x*-ray photographs, and physical examination should always be thorough before the *x*-ray is employed.

The *fluoroscopic* examination reveals movement, and when the lesion is well marked is of great importance, but in demonstrating the finer changes it is far inferior to good stereoscopic plates. These often reveal fewer changes than flat plates.

The early foci of infection are in the lymph masses at the division of the trunks. Because of these lesions the trunks may become thickened and extend from the inner through the middle zone, where they usually fade out, to the periphery. The small nodular lineal shadows which apparently invade the parenchyma of the lung have been called peritruncal tuberculosis. Similar shadows, which may be small or large, have sharp or indeterminate borders and are irregularly situated, are described as parenchymatous, and occur in nearly 98 per cent. of proved cases of tuberculosis. These are most helpful in diagnosis when situated away from the root zone, and above the third rib and third vertebral spine. Extensive pulmonary tuberculosis without even slight physical signs may be easily demonstrated by the *x*-ray, and in about 50 per cent. of cases such examination reveals more extensive disease than do the physical signs. If *x*-ray plates are made routinely whenever there is an acute upset, extension of the disease can frequently be detected before it is evidenced by physical signs. Slight indisposition during treatment may be thus demonstrated to be due to an advance of the disease. Serial *x*-ray plates taken at intervals of two, four, or six months provide a most valuable means of following the course of the disease.

x-Rays are of great value in excluding the possibility of pulmonary tuberculosis, but in very rare instances may demonstrate no lesions, although *tubercle bacilli* are present in the sputum. Slight lesions lying near or behind the heart may be overlooked. In streptococcal bronchopneumonia the *x*-ray picture may be the same as in pulmonary tuberculosis, but this condition is rare. Few other diseases cause fine or moderately coarse mottling above the third rib and third vertebral spine. In the detection of deeply placed cavities of either the honeycomb or annular type which produce no physical signs only *x*-rays are of value.

In some instances routine *x*-ray examinations, like routine physical examinations, reveal more or less well-marked and even extensive lesions which are probably tuberculous in individuals who have apparently never been ill. Such patients should be carefully watched, but do not require treatment.

Examination of Sputum.—The presence of at least three or four *tubercle bacilli* in the sputum, in the absence of demonstrable tuberculosis of the upper respiratory and alimentary tracts, is the only absolute proof of pulmonary tuberculosis. Failure to find *tubercle bacilli* in the sputum can be condoned, but failure to look for them admits of no excuse no matter how sure the diagnosis may appear. Although one positive examination outweighs dozens of failures, it should be confirmed at once. If there is no sputum, a specimen of mucus from the throat should be examined. Even clear saliva may contain *tubercle bacilli*, but the mucopurulent matter raised in the morning and the small amounts obtained at considerable intervals during the day are most likely to contain them. *Tubercle bacilli* may be found months before physical signs appear, and even before the *x*-ray demonstrates changes. They can sometimes be recovered from swabs from the pharynx, or from the stomach contents or feces when they are not present in sputum. Failure to find *tubercle bacilli* does not exclude the possibility of tuberculosis, and postponement of diagnosis until they do appear may preclude recovery. Their presence in the sputum is an indication of bronchial ulceration, and the number is of slight prognostic importance.

Patients should be instructed to bring the early morning sputum and the little dense balls raised at infrequent intervals. No sputum should be considered negative until three-day specimens have been submitted to concentration methods of examination. The blood in an initial hemoptysis may contain *tubercle bacilli*.

Macroscopical examination of a single specimen reveals little. As the disease progresses the sputum usually becomes more abundant, more purulent, and at times nummular and heavier than water. During improvement it becomes less and less purulent, and the color may change from green to yellow to white. Finally, no sputum or only small amounts are expectorated and the consistency becomes glairy. A sudden increase or decrease in amount suggests the onset of complications or acute miliary tuberculosis. The taste is at times salty or even nauseating. The sputum may be extraordinarily tenacious. In acute pneumonic tuberculosis it at first resembles that of pneumonia, but later becomes greenish.

The rather uncommon chalky concretions, called lung stones, are usually associated with the chronic disease. Before ejection they may cause fairly brisk hemoptysis. They arise in foci in the lung or glands, may be very

numerous, vary in size from a small shot to a cherry, are very irregular in shape, have rough projections, and rarely form in other diseases. The presence of elastic tissue in the sputum without *tubercle bacilli* is evidence against tuberculous infection. The various cellular elements, crystals, and casts of the bronchi are of interest.

Technic.—The best stain is carbolfuchsin, which may be heated on the slide or used cold overnight. Only new slides should be used. Acid alcohol is a satisfactory decolorizing fluid. Methylene-blue may be used as a counterstain, or Gabbett's solution after diagnosis has been made.

The only really certain method of differentiating *tubercle bacilli* from other acid-fast organisms is guinea-pig inoculation. When placed on the same slide and subjected to similar manipulations, however, *tubercle bacilli* usually retain the stain longer. Except in gangrene confusion rarely occurs. A mechanical stage greatly simplifies the search for *tubercle bacilli*. A slide should be examined for ten minutes before it is considered negative. The number of bacilli in each field should be noted, as a gradual decrease often indicates healing of the lesion. Very large numbers are usually found only when there are cavities.

Streptococci, staphylococci, and other inhabitants of the normal mouth are frequently found in tuberculous sputum. They appear to have no influence on the tuberculous lesion, but may be responsible for symptoms in the upper respiratory tract (bronchitis, tracheitis, rhinitis).

Of the many *concentration methods*, that of rendering the sputum homogeneous by the addition of equal parts of antiformin (15 to 50 per cent.) or NaOH (4 per cent.), incubation in the thermostat for fifteen to thirty minutes, shaking, and then centrifuging, is the most useful.

Tubercle bacilli have been cultivated from the sputum by Petroff's method when none were visible microscopically.

If injection of a single specimen of sputum into a guinea-pig does not cause infection the specimen probably contained no living *tubercle bacilli*. Three or four weeks after inoculation a tuberculin skin test should be performed, and at the end of six weeks the animal should be killed. It is possible that *tubercle bacilli* may be present in the sputum as well as in the urine in showers at infrequent intervals.

Roger has emphasized the presence of albumin in the sputum in tuberculosis as well as in other inflammatory pulmonary diseases except bronchitis.

The occurrence of closed pulmonary tuberculosis is now questionable. No doubt *tubercle bacilli* could be demonstrated in sputum more often than they are by prolonged and thorough search, but in many early and a few advanced cases the usual methods do not permit their detection in the sputum for months. Refusal to diagnose pulmonary tuberculosis until *tubercle bacilli* appear in the sputum is dangerous alike to patient and physician.

Urine.—The diazo and urochromogen reactions in the urine are often positive in late stages. Intracutaneous injection of small quantities of urine concentrated to one-tenth its volume often produces a marked but non-specific reaction. This test is of little diagnostic value.

Blood.—The complement-fixation test is the only serological method widely used. A positive reaction indicates that antigen (probably tuberculous poison) is or has recently been circulating in the blood, and, consequently, that some focus of infection is or has been open to the blood-stream,

and is not walled off or arrested. In 10 per cent. of patients with *tubercle bacilli* in the sputum the test is negative. It is helpful, but less reliable than the Wassermann test for syphilis. Its value depends largely upon the suitability of the antigen. The list of antigens, like that of tuberculins, is suspiciously long. Wassermann's new test for tuberculous activity needs confirmation.

Agglutination of *tubercle bacilli* and the "opsonic index" have proved of little practical value. In the sedimentation test the erythrocytes settle more rapidly than normal in tuberculosis as well as in syphilis, pregnancy, and tumor. The more advanced the tuberculosis, the more rapid the sedimentation. This is of slight diagnostic value, but, according to some, of considerable prognostic importance.

The Tuberculin Reaction.—Tuberculin has been used diagnostically in many ways, but today the cutaneous, intradermic, ophthalmic, perdermic, and the older subcutaneous tests are most frequently employed, the first two being the most popular.

In the literature a few facts are prominent. The tuberculin reaction occurs in man only after *tubercle bacilli* have gained a foothold in the body. A positive reaction is, therefore, an index of tuberculous infection. No tuberculin test accurately distinguishes active from inactive disease. A positive cutaneous test is likely to indicate activity in the first two or three years of life, but by puberty 40 to 75 per cent. of all children react positively. This test is supposed to be negative after measles, influenza, or in late stages of the disease, but probably the reaction is only deferred.

The technic of the *cutaneous test* is the same as that of vaccination. A drop or two of old tuberculin (25 per cent. or, preferably, full strength) is applied to a slight scratch through the epidermis. Physiological salt solution should be applied to a control scratch placed lower on the forearm. After five or ten minutes the fluid may be wiped off and the arm protected. At the end of one, two, or even four days in very ill children there may be seen a reddened, somewhat flattened papule, varying in diameter from 1.5 to 4 cm. This is rarely vesicular and is at times surrounded by a zone of erythema. It may last a short while or persist for weeks. In violent reactions even gangrene and sloughing may ensue.

Because the rate of cutaneous absorption may vary, and a negative reaction merely signify poor skin absorption, some physicians prefer the *intradermic test*. In this the tuberculin is injected so superficially that the lumen of the fine needle is visible through the epithelium. The volume of fluid injected should not exceed 0.3 c.c., and the initial dose of 0.0001 c.c. of old tuberculin should be increased until reaction occurs. Occasionally, possibly on account of faulty technic, the reaction is general.

The *ophthalmic test* consists in dropping into the eye 2 to 5 mgm. of precipitated old tuberculin in a few drops of physiological saline. If the eye is in any way diseased this test should not be employed, because at times the reaction is violent and produces much discomfort. It is doubtful whether this method differentiates active from inactive disease more accurately than do other tuberculin tests. It causes a reddening of the conjunctiva, especially about the caruncles, within two to twenty-four hours, which persists one or even three days when severe.

The *percutaneous test* is performed by rubbing into a small area of the skin a drop of old tuberculin or an ointment containing 10 to 50 per cent.

When positive, one or many small red papules appear after twenty-four hours. These persist for a few days.

The *subcutaneous test*, which has fallen very largely into disuse, is still of value in certain cases. The technic is simple. Old tuberculin is diluted aseptically with normal saline containing 0.25 per cent. phenol, so that successive doses of 0.0002, 0.001, 0.003, 0.005, and finally 0.01 c.c., repeated once, can be injected subcutaneously in the lower interscapular region or just below the insertion of the deltoid until a feeling of lassitude, malaise, and fever (temperature of 100° to 102° F., rarely over 104° F.) develop. The physical signs (usually râles) may also become more marked and the suspected pulmonary areas hazy in *x*-ray plates. *Tubercle bacilli* in rare instances appear in the sputum during or just after the reaction; they are not mobilized in the blood. The patient should remain in bed usually for one or two days until the symptoms and fever disappear. The diluted tuberculin should be placed on ice and not be kept for more than two weeks. It should be administered if possible in the evening and the patient should keep quiet or stay in bed the following day. If no reaction occurs the injection may be repeated after an interval of forty-eight hours.

This test should be employed only when no parenchymatous lesion, or at least one so small as to be doubtful, can be revealed by *x*-ray, and ought to be avoided if *x*-ray plates are not available. It should not be used when there is general glandular involvement, meningitis, heart disease, nephritis, epilepsy, Addison's disease, or fever (temperature of over 100° F.). In nervous patients a preliminary injection of physiological saline should be given. If employed only under these conditions the test is never dangerous. Many patients feel remarkably better after a positive reaction.

A positive reaction signifies only that tuberculin infection has taken place. A focal reaction indicates local involvement. If it is in the lung the patient should be treated for a while, but absence of focal reaction or, better still, absence of reaction to repeated injection of 0.010 c.c. of old tuberculin indicates that it is safe to continue work. Of the 41 patients who failed to react to this dose at Trudeau Sanatorium, none suffered later from pulmonary tuberculosis. Tuberculous patients also react to other substances, *e. g.*, diuretin, but only to much larger doses.

The Relative Value of Diagnostic Data.—It is often difficult to ascertain the correct significance of the numerous data which may seem unimportant when considered alone. At the Trudeau Sanatorium five criteria have been selected as of essential importance in determining the presence or absence of tuberculosis. These are:

1. The history or presence of pleurisy with effusion.
2. The history of hemoptysis (loss of 1 dram or more of blood).
3. The presence of moderately coarse râles above the third rib and third vertebral spine.
4. A parenchymatous change demonstrable by *x*-ray above the third rib and third vertebral spine, and, most important of all,
5. The presence of *tubercle bacilli* in the sputum.

Learn.

One or more of these criteria is necessary for a diagnosis of tuberculosis, and all must be absent to exclude such diagnosis. If only a history of effusion or hemoptysis alone can be obtained, a diagnosis of suspected pulmonary tuberculosis is justified; both together, however, are definite evidence of tuberculosis. At the Trudeau Sanatorium 264 patients, previously diag-

nosed as having pulmonary tuberculosis, were diagnosed after admission as non-tuberculous. One to seven years afterward only 2 had developed pulmonary tuberculosis.

None of these data is sufficient for a diagnosis of activity. While the localized symptoms and signs are of more value in determining the presence of tuberculosis, general symptoms, not due to other causes, are the important index of activity.

Clinical Activity.—Of the many laboratory tests devised to detect activity or reactivity in arrested tuberculosis none is of much value. Activity cannot be diagnosed until the symptoms are clearly apparent. Certain symptoms, such as fever, night-sweats, rapid pulse, and loss of weight and strength, are important, while others, such as cough, expectoration, or even at times hemoptysis, are less significant. Physical signs are usually of value only when observed repeatedly at intervals of one or two months; but lesions, which reveal cottony shadows on stereoscopic plates, are likely to be active or to have been so recently. *x*-Ray studies made at rather frequent intervals (two months), like repeated monthly physical examinations, may indicate advance of a process not otherwise discoverable. In other words, physical signs and *x*-ray shadows are evidence of what has taken place, symptoms of what is taking place.

Rapid Examination.—It is at times necessary in industrial or army work to examine large bodies of men in a relatively short time. They should be stripped to the waist, given cloths to cover their mouths, instructed how to cough, and questioned about exposure to tuberculosis in the family or during work, and the occurrence of hemoptysis or pleurisy. Any one of these three data indicates the need of a special examination later. If there has been no exposure or suggestive history the physician should hastily examine the chest by placing the stethoscope on three or four places on each side of the front and back. Such superficial examination reveals a large number of the more pronounced cases. These as well as all suspicious cases must be examined more fully later.

Diagnosis of Special Forms.—In acute tuberculosis, either primary or superposed upon a more chronic process, with high temperature, rapid pulse, hurried respiration, and perhaps considerable cyanosis, the physical signs may be slight or show no change for some days. When diagnosis by any means is difficult, and tuberculosis is suspected, the condition is called latent. The minimal stage is the earliest in which a positive diagnosis can be made. Recognition of the advanced form, with involvement of both lungs and often other parts, offers difficulty only when *tubercule bacilli* are hard to find.

In childhood more attention has recently been paid to intimate exposure, malnutrition, pallor, lassitude, and fretfulness. The physical signs and *x*-ray findings more or less closely resemble those of adults. Some consider râles in the inner fourth and fifth interspaces very suggestive.

Differential Diagnosis.—The diseases which may be confused with pulmonary tuberculosis can be divided into two groups—those which pulmonary tuberculosis may simulate and those which simulate pulmonary tuberculosis. In the first group belong typhoid fever, nervous dyspepsia, chlorosis, neurasthenia, and such pulmonary affections as chronic bronchitis, influenza, asthma, and acute and chronic pneumonia. In the second are latent infection (including endocarditis, sinusitis, pyorrhea alveolaris,

alveolar abscess, chronic tonsillar infections), pernicious anemia, hyperthyroidism, mitral stenosis, neuroses, psychoses, effort syndrome, and a number of pulmonary conditions, such as influenza, bronchiectasis, abscess, syphilis, Hodgkin's disease (especially of the Pel-Ebstein type), tumor, actinomycosis, infarct, chronic basal conditions, spirochetosis, aspergillosis, the presence of foreign body in a bronchus, amebiasis, and pneumoconiosis.

When *tubercle bacilli* are absent it is important to bear in mind the possibility of such conditions, but application of the essential diagnostic criteria of pulmonary tuberculosis and of the disease under consideration usually quickly determines the diagnosis.

Acute tuberculosis may closely simulate typhoid fever, and on account of the importance of treatment every effort should be made to obtain immediately a definite diagnosis. *Streptococcal pneumonia* with râles and *x*-ray changes in the upper lobe is at times very confusing. Diagnosis may depend upon the sputum examination and repeated examinations. *Chronic asthma* may be the result of old tuberculous lesions. Syphilis with more or less fever and slight changes in the physical signs is often confusing, but careful *x*-ray study usually permits differentiation. *Bronchiectasis* with frequent hemoptyses can often be excluded by the long history, basal changes, and *x*-ray findings. Acid-fast organisms, not *tubercle bacilli*, have been found in *pulmonary gangrene*. *Actinomycosis* often involves the extrapleural tissues, which is unusual in tuberculosis. Tumor may often be diagnosed by collapsing the lung or replacing an effusion with air, and then taking an *x*-ray photograph or using thoracoscopy. *Cardiac disease* may produce râles at an apex.

Lawrason Brown.

Fibroid Tuberculosis

In all types of tuberculosis except the very acute there is a proliferative tissue response leading to the formation of fibrous tissue within and around the foci of infection. It is essentially an expression of healing of the tuberculous process. In a comparatively large number of cases of chronic ulcerative pulmonary tuberculosis this fibroid change becomes the predominating characteristic of the morbid anatomy. Fibrous tissue also develops within a lung long compressed by either a pleural effusion, air, or by operative procedures (extrapleural thoracoplasty).

In the majority of cases the upper third of the lung is concerned in the fibroid change, but the whole lung may become involved in the process. The extensive fibrous tissue causes the lung to shrink and to become leathery. The pleura is practically always involved in fibroid tuberculosis. It becomes thickened and adherent—a change which may involve the whole pleura surrounding the lung, and in itself be a factor in causing shrinkage of the lung. A dense-walled cavity is often found in the upper third of the lung, and elsewhere there are encapsulated cheesy deposits. As a result of the fibrosis and lung shrinkage the bronchi are frequently dilated and become the seat of a bronchiectasis.

Symptoms.—Not infrequently a fibroid apex is discovered accidentally or during a routine examination, the patient being unaware of its existence. Those patients who develop a fibroid lung as the end-result of a chronic ulcerative tuberculosis may live for many years in good health, with only cough, expectoration, and shortness of breath on exertion as symptoms of

respiratory disease. The expectoration is often profuse and purulent. There may be recurring hemoptyses. Individuals with extensive pulmonary fibrosis are often thin and "wiry." Death may be caused by a severe hemoptysis, or by a gradual extension of tuberculosis into the sound portions of the lungs.

Physical Signs.—The affected side of the chest is flattened and its motion limited. Often the shoulder on this side is lower than its mate. The heart is displaced toward the diseased side, its pulsations being visible over a wide area. Palpation of the trachea in the suprasternal notch will find it drawn over toward the fibroid lung. The tactile fremitus may be diminished or increased, depending upon the amount of pleural thickening and the extent of underlying pulmonary consolidation. The percussion note is dull over the front and back, especially in the upper half. Bronchial breathing is heard over the areas of fibroid consolidation. There is cavernous breathing if a cavity is present. At the base of the lung the breath sounds are usually feeble and bronchovesicular in type. Râles may be few and dry in character.

If tubercle bacilli are constantly absent from the sputum the diagnosis of fibroid tuberculosis at times becomes extremely difficult because pulmonary fibrosis caused by such factors as pneumokoniosis and bronchiectasis may simulate fibroid phthisis in symptoms, physical signs, and *x*-ray findings.

The diagnosis of the condition rests upon the occupation of the patient (dusty trades favoring pneumokoniosis), the history and symptoms, and the presence or absence of tubercle bacilli in the sputum after repeated examination or animal inoculation.

EDWARD N. PACKARD.

COMPLICATIONS OF PULMONARY TUBERCULOSIS

I. Upper Respiratory Tract.—(*a*) The *larynx* is a very common site for the development of a tuberculous lesion secondary to the pulmonary involvement. The frequency with which the larynx is invaded increases with the progress of the pulmonary disease. St. Claire Thompson's figures show a 5 per cent. involvement in the earliest stages, 18 per cent. in the more severe cases, and in the advanced group 32 per cent. Fetterolf, in a microscopical study of 100 fatal pulmonary cases, found the larynx involved in 83.

The site earliest attacked is commonly the interarytenoid space, the anterior surface of the arytenoid bodies, and the vocal processes. The vocal cords come next, while tuberculosis of the epiglottis is generally a late extension of the disease.

The first symptom is usually slight but persistent huskiness of the voice. Pain in the larynx or the sides of the throat indicates extensive involvement, while pain and difficulty in swallowing occur when the epiglottis is infiltrated, edematous, or ulcerated. Although laryngeal tuberculosis is one of the most serious complications of pulmonary tuberculosis and beclouds an otherwise favorable prognosis, nevertheless it does not necessarily foretell an early fatal issue as formerly believed. In its early manifestations and, at times, late stages it is often amenable to proper treatment (voice rest, galvanocautery). A larynx may improve or get well, while the lung disease remains quiescent or gets worse; but if the disease in the larynx advances, the chance for arrest of the pulmonary disease is poor.

(*b*) The *pharynx* may become involved by extension from a tuberculous larynx. Small whitish tubercles beneath the mucosa coalesce and break down to form a tuberculous ulcer. The spreading ulcer is rarely, if ever, checked, and is extremely painful, so that the swallowing of food is difficult or impossible. It inevitably leads to an early fatal issue.

(*c*) *Tuberculous ulceration of the tongue* is seen in less than 1 per cent. of all pulmonary cases.

II. **Lower Respiratory Tract.**—(*a*) *Bronchiectasis* is not an infrequent accompaniment of advanced pulmonary tuberculosis, especially if extensive fibrosis is present. It may be the source of much purulent sputum, at times colored with blood.

(*b*) *Emphysema of the lung tissue* not actually involved in the tuberculous process is often met with, notably in long-standing fibroid cases, where, with the gradual shrinkage of the fibrous parts, the healthy portions of the lungs hypertrophy.

(*c*) *Extensive gangrene of the lung* is very rare. Foul breath and fetid sputum may arise from gangrenous shreds on the walls of a cavity, or from infection with putrefactive organisms.

(*d*) *Non-tuberculous pneumonia* is an uncommon complication of active pulmonary tuberculosis. There have been only 2 proved cases among 5000 tuberculous patients treated at Trudeau Sanatorium.

(*e*) *Inflammation of the pleura accompanies all types and stages of pulmonary tuberculosis.* The area of inflammation may be small or it may involve the whole pleural surface. The fibrinous deposit produced by the inflammation may organize and form adhesions between the visceral and parietal pleura, or it may be absorbed and the pleura return to its natural state. Frequently an effusion forms. As pointed out by Osler, a pleurisy with effusion is more likely to precede than to accompany pulmonary tuberculosis. These effusions may be blood-tinged, serous, or purulent. Bloody effusions are rare in chronic phthisis; serous effusions are the most common; while purulent effusions occur chiefly as a complication of pneumothorax.

(*f*) *Pneumothorax* occurs in about 5 per cent. of all cases of pulmonary tuberculosis. It rarely if ever complicates fibroid tuberculosis or acute miliary tuberculosis. The pneumothorax is produced by air from the lung entering the pleural "space" through a ruptured caseous subpleural tubercle, or through a tear in the wall of a cavity located directly beneath the pleura. The pneumothorax may be general or localized, that is, the lung may be completely collapsed or only partially so, depending upon the presence or absence of pleural adhesions. Pneumothorax may take place without symptoms, but usually the local and constitutional reactions are immediate and most severe, and death may follow in a few hours or days after the collapse of the lung. If the patient survives the initial shock there are two probable outcomes—either the rupture closes, the air in the pleural cavity is absorbed, and the lung re-expands, or the tear in the pleura remains patent, the pleuræ become infected, a purulent effusion forms (pyopneumothorax), and death eventually ensues. Although pneumothorax may occasionally be of benefit by collapsing a diseased lung, nevertheless in the great majority of instances it is a most serious and dangerous complication.

(*g*) *Mixed Infection.*—The finding of other organisms besides the tubercle bacillus in the secretions of cavities and bronchi, coupled with the

symptoms of septic infection, such as high fever with daily remissions and sweats, has led some to believe that the ulcerative stage of pulmonary tuberculosis is largely the result of this secondary invasion of tuberculous tissue. Experiment, however, has shown that the tubercle bacillus alone can produce the pathological and clinical picture above mentioned; that cultures from cavities have often been sterile and that the secondary organisms, when found, have proved of low virulence; hence the finding of these organisms in and around tuberculous tissue is no proof that their presence is the cause of the ulceration or of the clinical picture.

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TUBERCULOSIS OF THE ALIMENTARY TRACT

Mouth.—Lesions of the mouth are practically always secondary, although a few are reported without disease elsewhere in the body.

Tongue.—Tuberculosis of the tongue first appears as a lighter shaded area or as a group of small granulations on the dorsum, margin, or tip of the tongue. The lesion is generally single and quite painful. The mucosa becomes indurated and an ulcer forms which tends to extend eccentrically. There is usually no definite enlargement of the lymphatic glands which drain the ulcer—an important point in the differential diagnosis. The lesion, as a rule, extends without much induration, although there may be rather dense thickening of the tongue in the advanced stages. Dysphagia results from pain, which toward the end becomes intense and is alleviated only partially by cocain or morphin. That the necrotic material from the base of the ulcer usually contains tubercle bacilli may be demonstrated either in smears or by guinea-pig inoculation. Biopsy should only rarely be necessary. A very unusual form of tuberculosis of the tongue begins as an abscess in its substance.

Pharynx.—In severe cases, especially in those of laryngeal involvement, the tuberculous infection may spread to the pharyngeal walls and even to the soft or the hard palate. Such conditions are very distressing.

Tonsils.—Weller in 1921 made an exhaustive study of the incidence and histopathology of tuberculosis of the tonsils, and found that of the 8697 tonsils examined, 204 (2.35 per cent.) contained tubercles, a figure which would probably have been increased slightly by different technic. Other investigators have discovered tubercles in between 0.3 and 8 per cent. of tonsils examined. Cryptic infection seems to be the most common type, but there were also ulcerative lupus-like lesions formed by coalescence of the cryptic infections or by direct extension from neighboring surfaces, and also a diffuse bilateral miliary tuberculosis, the lesions of which were situated almost entirely in the follicles and germ centers.

Clinical recognition of tuberculosis of the tonsil is almost impossible because, unless there is suppuration, no characteristic signs or symptoms develop. The tonsil may atrophy, undergo hypertrophy and project from the wall of the throat, or be almost hidden within the pillars. The pharyngeal tonsil may also be involved, either alone or with one or both faucial tonsils.

Weller found 182 cases in which both faucial tonsils could be examined. In these the lesions were unilateral 133 times, bilateral 49 times. Of the 26 examinations of all three tonsils (faucial and pharyngeal), 2 showed the lesions to be triple, 4 double, and 20 single.

The tonsil is to be regarded as the most important portal of entry of the bacillus in tuberculosis of the cervical glands, although tonsils frequently fail to contain tubercles when they are present in the lymph-nodes. The converse is true sufficiently often to render advisable the removal of tonsils in tuberculous adenitis in order to eliminate a possible source of further infection.

Esophagus.—Lesions in the esophagus are exceedingly rare. They may originate as a blood or lymph infection or may spread from the larynx or pharynx. Perhaps most commonly the esophagus is involved by extension from neighboring peribronchial or mediastinal glands.

Stomach.—Tuberculosis of the stomach is a rare condition associated more commonly with miliary than with pulmonary tuberculosis. The digestive disturbances which occur so frequently in tuberculosis and which may even be the first symptom very rarely result from direct involvement of the stomach, but are usually caused by the toxemia, fever, enforced rest, overfeeding, and effect of drugs upon the gastric function. The low incidence of tuberculous ulcers in the stomach is peculiarly interesting in view of the fact that such ulceration practically always takes place during the terminal stages of pulmonary tuberculosis (0.4 to 0.8 per cent. of autopsies).

Liver.—The liver, strictly speaking, is practically always involved in chronic pulmonary tuberculosis, and is obviously extensively infected in acute miliary tuberculosis. In the chronic forms of the disease it must, on account of its generous blood-supply, receive large numbers of bacilli which are transported from time to time in the blood-stream; and in such cases microscopical study of the hepatic tissue at autopsy almost always reveals the presence of small, discrete, fairly typical tubercles and only a few bacilli. The large solitary tubercle may be found or, much more commonly, tuberculosis of the bile-ducts, which is really a suppurative angiocholitis. The tuberculous nodules become softened and stained with bile. Bacilli are usually rare. The necrotic areas may attain the size of a cherry, but are ordinarily microscopic. Fatty amyloid degeneration is evident, but not specific. Various cirrhoses are also found. Hanot and Gilbert have described atrophic and hypertrophic forms, with and without ascites, with prolonged or temporary icterus, but these conditions are not characteristic and cannot be distinguished from cirrhoses due to other causes. Jaundice is quite uncommon and, when present, is usually of a mild grade.

Intestines.—Most intestinal tuberculosis is secondary to tuberculosis of the lungs, and while the lesions are caused chiefly by swallowed bacilli, many are of hematogenous origin. The condition may also be a primary infection, usually in children. Rarely it results from perforation of a tuberculous mass from without inward. In children intestinal tuberculosis is most common from the third to the eighth year. The mesenteric lymph-nodes are more frequently involved than the intestines, though the two are usually associated.

Morbid Anatomy.—In a series of 386 autopsies upon tuberculous children (the majority under three years of age) Holt found intestinal tuberculosis in 40 per cent. The lesions were usually of minor importance. Autopsies of tuberculous adults show a very high percentage of intestinal involvement. Heinze found intestinal lesions in 51 per cent. of 1226 autopsies on patients with phthisis. Weigert and Orth found them in 90 per cent. of such cases.

Infection begins in the lymphatics. According to Aschoff, there is first a formation of subepithelial tubercles, most frequently in the lymph apparatus of the lower ileum. Peyer's patches are often involved. As necrosis develops the lesion breaks through into the lumen of the gut and an ulcer forms. Coalescence of small ulcers produces the larger type. These are usually located transversely in the intestine and may form a ring, but may also lie along the axis of the intestine. The margin of the ulcer is irregular, infiltrated, and often caseous. The submucosa and muscularis are involved, and in the serosa tubercles may project from the intestinal surface. Perforation rarely occurs, probably because the slow approach of the lesion to the surface allows the threatened area of the serosa to form fibrinous adhesions to other peritoneal surfaces. Strictures may develop. The lesions are chiefly in the ileum, cecum, and colon. There is a not uncommon form of hyperplastic ileocecal disease, a localized chronic inflammatory process, which often involves the appendix. The tumor-like mass which may form sometimes suggests a carcinoma.

In the rectum the disease assumes the simple ulcerative form with infiltration and occasionally stenosis. Fistula *in ano* occurs in 3.5 per cent. of cases of pulmonary tuberculosis according to Osler. When unexplained the condition should always direct attention to the lungs. The pulmonary involvement is said to progress rapidly unless a tuberculous perirectal abscess is thoroughly cleaned. The author's experience is that simple incision of such lesions is the best procedure during an active pulmonary tuberculosis.

Symptoms and Diagnosis.—Tuberculosis of the intestines has always been one of the most dreaded complications of this disease. Diagnosis was formerly very unsatisfactory and the classical symptoms of protracted diarrhea, abdominal pain, tenderness, and rigidity were either misleading or a sign of far-advanced and hopeless lesions. Tubercle bacilli were sought in the mushy or watery stools, although many observers had demonstrated that they are present in the feces of practically every open pulmonary case. Microscopical blood was looked for, but rarely found; occult blood was more frequently demonstrated. Pus-cells were present only when there was much necrosis of the lesions. All in all, the difficulties and uncertainties were so great that many excellent clinicians would rarely make the diagnosis.

More recently this state of affairs has undergone a decided change. Stierlin and Pirie have both called attention to certain filling defects in the ulcerated intestine which are demonstrable by the *x*-ray after ingestion of bismuth or barium; but it is to Lawrason Brown and H. L. Sampson that we are chiefly indebted for the perfection of a method of diagnosis and for its emphatic introduction to the medical profession. These workers do not yet claim to diagnose tuberculosis of the small intestine, but many well-controlled data demonstrate that as a means of diagnosing lesions of the colon their procedure, properly employed, is as nearly infallible as any modern methods of examination. It depends upon the fact that an ulcerated area of intestine is hyperirritable and does not tolerate the presence of the test-meal within it; the diseased portion of the intestine contracts in an effort to expel the test material; thus there is an absence of opacity in the diseased area which contrasts with the normal filled intestine. The detailed technic of the method is described in the original articles of Brown and Sampson. One great advantage of such examinations is that they permit very early diagnosis while treatment may still be effective.

With this improved diagnosis has come a better comprehension of symptoms. Diarrhea is usually a late manifestation, and constipation may be the rule for some time after the onset. There may be no abnormal symptoms in the beginning, simply an unexplained low fever or loss of weight. Such a manifestation is so common that the intestines should always be examined when, in pulmonary tuberculosis, fever and loss of weight become unduly marked. Although abdominal symptoms are present, they may be surprisingly mild—only chronic indigestion and more or less flatulence.

Familiarity with this form of *x*-ray examination renders it more and more useful, particularly since various methods of radiation seem to benefit tuberculosis of the intestinal tract. With this new method at hand, appendectomy should never be performed during pulmonary tuberculosis until the possibility of tuberculosis of the ileocecal region has been excluded. The latter may produce all the symptoms of appendicitis, even to the high white cell count.

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TUBERCULOSIS OF THE BRAIN AND CORD

The formation of discrete tubercles in the substance of the brain is somewhat less common than tuberculous meningitis. These lesions may be very numerous and miliary in type, or large, and occur singly or in relatively small numbers. The so-called *solitary tubercle* begins as a miliary lesion in the covering of the blood-vessel, extends into the substance of the brain, and eventually becomes almost any size. Such lesions are quite clearly defined, but cannot be readily enucleated. The smaller tubercles of this type, either single or multiple, are not at all uncommon in children, and, indeed, constitute more than 50 per cent. of the brain tumors in children according to some observers. They seldom develop in the aged, and are always secondary to manifest or latent tuberculosis elsewhere in the body. Solitary tubercles most commonly develop in the vascular regions, such as the fissure of Sylvius, the pacchionian bodies, the pons, the cerebellum, and the medulla oblongata.

Symptoms.—The symptoms are those of tumor, and while barely sufficient to permit definite diagnosis, may be supplemented by the presence of tuberculosis in other parts of the body. The disease progresses slowly with intermissions, continuing perhaps for several months. Death may take place during convulsions or be hastened by meningitis.

Tuberculosis of the dura mater (*pachymeningitis*) may complicate disease of the bones of the head, sinuses, petrous portion of the temporal bone, or calvarium. A mass is eventually formed which produces the symptoms of brain tumor; the spinal fluid is normal, and only caries of the bone suggests the diagnosis.

Solitary tubercles of the cord are seen very rarely. Most tuberculous lesions of the cord and its envelopes develop in the course of Pott's disease and are due to an extension from the diseased vertebræ. The slow evolution of the lesions generally gives time for the arachnoid and pia mater

to become adherent. The bacilli contained within the adhesions are then shut off from the subarachnoid space, and the cord may thus become diseased without any generalized spinal meningitis. For the same reason, according to Sicard, the cerebrospinal fluid is usually normal. The lesion is essentially an external pachymeningitis, from which result the pressure determining degeneration of the cord and the symptoms dependent thereon.

TUBERCULOSIS OF THE GENITO-URINARY SYSTEM

Tuberculosis of the genito-urinary tract, particularly of the *kidney*, has been widely studied in recent years, and has come to be better understood. Infection may take place in a negligible minority of cases by direct extension, but it is most often carried in the blood. Controversy still reigns as to the incidence of bacillemia, but all observers agree that tubercle bacilli do at times enter the circulation, and are either destroyed in the blood or lodge in the tissues, vessels, or lymphatics. The more recent demonstrations of the phenomena of allergy as applied to various organs also throw new light upon many early observations.

Urogenital tuberculosis, like that of the lungs, occurs most frequently between the ages of twenty and forty years and affects males more frequently than females.

Tuberculosis of the Kidneys.—Infection may very exceptionally pass through the ureter upward to the kidneys, or, as has been claimed, through the peri-ureteral lymphatics; but recent observers agree that the blood-stream is by far the most common source of infection. Bacilli are arrested either in the glomeruli or in the terminal branches of the renal artery in the cortex, and may there initiate the formation of tubercles. Infection of the renal medulla is probably produced by tubercle bacilli carried in the cortical lymphatics toward the hilum of the kidney.

The rarity of tuberculosis of the kidney of sufficient severity to demand operation, and the frequent presence of albumin, casts, and red blood-cells in the urine of patients without symptoms suggestive of any renal involvement is very striking. There has been considerable controversy as to whether these urinary findings are really an indication of renal tuberculosis. Hobbs has recently concluded that about 50 per cent. of patients with chronic pulmonary tuberculosis have some degree of albuminuria; this is usually slight, and may or may not be associated with tuberculous changes in the kidneys. He also believes that the amount of albumin present is more closely related to the degree of pulmonary disease and pyrexia than to the presence of renal lesions. Albuminuria need not accompany tuberculosis of the kidney, and is, therefore, not pathognomonic of that condition. Casts, too, are often present when the kidney is not infected; various observers have found them in the urine of a fairly large percentage of patients with pulmonary tuberculosis—10 to 50 per cent.—according to the severity of the pulmonary disease. The small number of red cells found in the urine of 46 per cent. of subjects did not appear indicative of renal tubercles. A few pus-cells are very often present; when at all abundant the sediment should be examined for bacilli.

The finding of tubercle bacilli in the urine of individuals without symptoms referable to the genito-urinary tract has also given rise to much discussion. Among 100 cases of pulmonary tuberculosis Bernstein demonstrated tubercle bacilli in the urine of 10 by guinea-pig inoculation. Lawrason Brown

had 10.5 per cent. of positive findings in one series of 100 cases and 3.8 per cent. in another series of 52 cases. Cunningham's results were positive in 9 per cent. of 66 cases. When the urine is examined during advanced stages the percentage is much higher (50 per cent. or more). Of the six positive examinations made by Hobbs on 100 patients, two were on individuals who came to autopsy; one had a small caseating area in the kidney, but the other showed no evidence of renal tuberculosis. As Hobbs suggests, more positive results would probably have been obtained had the urine been examined more frequently and in larger quantities. From these data it may be concluded that tubercle bacilli are sometimes excreted by kidneys in which there are no actual tubercles, at least of a size to necessitate surgical intervention.

The views of Rist and Leon-Kindberg on the kidneys of tuberculous patients accord with the present conception of tuberculous disease and bodily resistance to it. They recognize that four conditions are possible: (1) Absence of bacillemia, when the kidney is normal, shows evidence of amyloid degeneration, or is affected by amyloid degeneration in other viscera; (2) the occurrence of bacillemia, with almost complete immunity in the body, particularly in the kidney, destruction of most of the bacilli, a few of which are excreted, and the absence of macroscopic or microscopic renal lesions, although inoculation of a fragment of kidney may produce a positive result; (3) the development of various types of lesions, large tubercles, miliary tubercles, tuberculous infiltration, etc., when the immunity is less complete or the amount of infection brought to the kidney is very great, or fairly intense reaction of the connective tissue if the relative immunity is sufficient; (4) an allergic reaction sufficiently intense to cause death with almost no clinical manifestation, when there is very marked hypersensitiveness and when a large number of bacilli pass to the kidney, or acute terminal hemorrhagic nephritis. It is not at all uncommon during phthisis for an aggravation of symptoms to occur, with edema and hematuria—the transient hemorrhagic nephritis of tuberculous individuals.

Excision of the kidney is obviously made necessary by the development and extension of one or more small tubercles. These increase in size and extend by contiguity or, more frequently, by lymphatic channels. The medulla of the kidney may become involved in a necrotic process which breaks into the pelvis.

Symptoms.—Since walled-off deposits in the renal parenchyma probably cause no symptoms until they extend to the pelvis of the kidney or perinephric tissue, the appearance of symptoms may at times be long delayed. As soon as pus and necrotic material gain access to the kidney pelvis, however, the ureter and bladder usually become infected and symptoms make their appearance. Micturition is frequent and later becomes painful. The first symptom may be hematuria. Dull aching pain in one lumbar region is frequently complained of. Pus, blood, and tubercle bacilli are present in the urine if the renal lesion is draining. The ureter has a tendency to stricture, and there may be temporary blocking off and cessation of drainage which produces an intermittency in the urinary findings.

Diagnosis.—Acid-fast bacilli in the urine are usually human tubercle bacilli, but *Smegma bacilli* are present now and then. Guinea-pig inoculation is the only really sure method of differentiation. In a series of 1324 routine urinalyses at the Saranac Lake Laboratory during 1923, 15 speci-

mens were found to contain acid-fast bacilli which failed to infect guinea-pigs. It is noteworthy that 14 of these were in women. Most of the patients had pulmonary tuberculosis and smears of urinary sediment were made on account of the large number of pus-cells present. The majority of these patients have been under observation several months since the acid-fast bacilli were seen, and not one has shown any evidence of genito-urinary tuberculosis. The avian type of tubercle bacillus very occasionally attacks the kidney and may be eliminated in the urine in large numbers. Too often acid-fast bacilli which fail to infect the guinea-pig are said to be *Smegma bacilli* without further question.

Cystoscopy is an invaluable aid to diagnosis and indispensable in the decision of the advisability of operation for renal tuberculosis.

Treatment.—For chronic unilateral disease operation is generally necessary. With involvement of both kidneys, and when there is active disease elsewhere, it is very difficult to determine the most suitable type of therapy.

Tuberculosis of the Ureters and Bladder.—Disease of the renal pelvis may extend into the ureter, causing ulceration of the mucous membrane alone, or a condition in which the tube is thick, hard, adherent, and tends to contract rather than to dilate. The latter lesion may develop above a stricture.

Tuberculosis of the bladder is practically always secondary and most often follows disease of the kidney. When of renal origin it begins in the mucous membrane about the mouth of the ureter on the diseased side and spreads to the base and posterior wall. Occasionally it is secondary to tuberculosis of the testis, seminal vesicles, or prostate gland. Increased frequency, painful micturition, pyuria, and hematuria are common symptoms, and should always suggest tuberculosis when they persist unexplained without apparent reason for any length of time. Cystoscopy should determine diagnosis.

Tuberculosis of the Male Genital Organs.—While the relationship of genital tuberculosis in the male to disease of the bladder and kidney is not entirely known, the genital and urinary system may be regarded as separate. Baumgarten showed experimentally that infection travels always with the secretion current and never against it; that is, infection will not travel from bladder to testis, but may take the reverse direction, infecting the seminal vesicles and prostate en route. Infection of the testis is generally blood-borne and begins in the epididymis, later involving the testis itself, the seminal vesicles, and prostate gland. The lesions are more often unilateral, only about 50 per cent. or less of patients showing bilateral changes. The testis and epididymis are involved in about 50 per cent. of cases of urogenital tuberculosis. The disease usually develops during the period of greatest sexual activity, although childhood and old age are not entirely spared. The process may extend to the bladder.

Tuberculosis of the seminal vesicles is fairly common and Teutschlaender goes so far as to say that of the male genital organs these are the most frequently involved. The lesions are unilateral in about one-third of cases.

The prostate derives its infection possibly from both urine and semen, and since it also receives blood-borne infection is involved in many cases (25 to 100 per cent.) of genito-urinary tuberculosis. These organs should be examined routinely in all cases of suspected tuberculosis.

Tuberculosis of the Female Genital Organs.—Pankow, after summarizing the figures of a number of German pathologists, states that there is evidence of genital tuberculosis in between 2 and 3 per cent. of all female cadavers. The incidence is highest at the period of greatest sexual activity—*i. e.*, during the third decade of life—but the disease may occur in children.

Recent work tends to indicate that the fallopian tubes are the part of the genital tract most often involved. In the many cases reviewed by Pankow these were affected in about 84 per cent.; the uterus, in about 50 per cent. Approximately 50 per cent. of all examinations revealed simultaneous infection of both.

Infection is almost always secondary, and in the tubes is probably derived from the blood. Genital tuberculosis is rarely acquired by direct contact, cohabitation, or extension of the disease from the intestine and bladder. Just how frequently it spreads from the peritoneum is unknown.

Tuberculosis of the fallopian tubes is usually bilateral. Macroscopically characteristic lesions may not be found, and the changes may resemble those of the late stages of sepsis or gonorrhea. Gross section may reveal tuberculous nodules, but microscopic examination must often be employed to demonstrate the tuberculous nature of the infection.

Tuberculosis of the Ovary.—The ovary is involved only secondarily. The nodules are usually superficial and rarely invade the ovarian tissue.

Tuberculosis of the vagina is rare. The lesion is an ulcer with a dirty purulent base, which does not bleed easily.

Tuberculosis of the placenta is rare, but Schmorl and others have demonstrated that it probably occurs more frequently than is generally believed. The lesions, which are often found only after exhaustive search, have been seen in the placentæ of women with advanced tuberculosis, as well as in those with only early and mild infection.

Tubercle bacilli probably pass through the placenta from mother to fetus very rarely. Warthin and his co-workers have, in three years, observed 3 cases of placental tuberculosis in patients without clinical manifestations of the disease. Only one of these women later showed symptoms of tuberculosis. None of the children, so far as has been learned, became tuberculous. Warthin favors the belief that fetal tissues are inherently resistant to the tubercle bacillus.

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THE PROGNOSIS IN TUBERCULOSIS

Any prediction of recovery from tuberculosis must be made with caution. It is rarely safe to base the prognosis upon clinical, laboratory, or *x*-ray findings. In few diseases does recovery depend so much on the attitude of the patient; in pulmonary tuberculosis the road to health is long and tedious, and the patient must make up his mind to follow a strict régime for many years. As relapses are apt to occur even after apparent recovery, the patient's mode of life and routine of daily activities must be carefully regulated. Age has an important influence on the outcome of the disease; in the first few years of life recovery is rare and adolescents are less resistant than those of more mature age. If the disease is recognized in the early stages while the lesion is still small, faithful treatment and careful observation can often prevent exacerbation and thus render the possibility of recovery much greater.

According to the Trudeau Sanatorium reports death from tuberculosis took place within six years in about 60 per cent. of the early cases, in 75 per cent. of the moderately advanced, and in 90 per cent. of the far-advanced ones. Lawrason Brown makes the statement that three or four years are necessary for complete cure of tuberculosis, and that the reason so many die is because they do not realize this fact. Of 2651 patients with pulmonary tuberculosis who were traced by nine sanatoria, only 49 per cent. were alive at the end of five years, only 26 per cent. at the end of ten years, and only 15 per cent. at the end of fifteen years (Waring).

Artificial pneumothorax and surgical collapse of the chest have often proved to be curative measures when the condition seemed hopeless. Tuberculous pneumonia as well as pulmonary tuberculosis may yield to such treatment. The *laryngeal* and *intestinal complications* of pulmonary tuberculosis are not as dangerous as was formerly thought, but do reduce the chance of recovery. The general optimism about the outcome of *pleurisy with effusion* is hardly justified. In some cases when the progress is very good *tuberculous meningitis* suddenly develops, or *hemoptysis* takes place unexpectedly. Poverty and neglect frequently allow the disease to run its course unhindered.

THE PROPHYLAXIS OF TUBERCULOSIS

Immunity to tuberculosis can be produced in experimental animals only by infection with *tubercle bacilli*, a procedure which is too dangerous and uncertain to be generally employed for the protection of man. Absolute cleanliness, isolation of all consumptives, sterilization of their sputum, and

pasteurization of all milk from tuberculous cattle might possibly blot out the disease, but it is probable that civilized man can never escape infection with the *tubercle bacillus*. Prophylaxis is, therefore, a matter of early recognition and treatment of the disease in order to prevent, in so far as possible, any spreading of the lesion. It has been estimated that at least 1 per cent. of all human beings have active pulmonary tuberculosis and that many of these expectorate *tubercle bacilli*.

Since children are particularly susceptible to the disease, they must be kept away from infected individuals and sources of infection, particularly at home. An infant born to a tuberculous parent should, if possible, be taken from the home at once. That such a measure is desirable has been definitely proved by results obtained by the *Œuvre Grancher* in France, after placing the children of tuberculosis parents in healthy families in the country districts. Preventoria, nutrition camps, and open-air schools are also of great help in reducing the incidence and spread of the disease.

In order to reduce the incidence of serious tuberculous infection children should be submitted to the skin tuberculin test once a year. As the first six months after infection are critical, it is desirable to carry out such routine examinations which would reveal the infection in most cases before it had become wide-spread, and would permit the establishment of a suitable régime. Neglect of the very early signs of tuberculosis both by the patients themselves and by physicians accounts in large measure for the severity of much tuberculosis. Because observations made during and after the World War have demonstrated the marked effect of mental and physical fatigue and privation in reducing the resistance to latent tuberculous infection, the need for careful supervision of the hygiene of children is coming to be more and more fully appreciated. Even when there is no sign of tuberculosis the period of convalescence from infectious diseases should be somewhat longer than was formerly deemed necessary, and special attention should be paid to the condition of the teeth, tonsils, and adenoids. Should the von Pirquet skin test be positive, the child must be watched with unusual care and undergo special examination.

The course of the temperature during rest should be determined, and the condition of the chest ascertained by means of the *x*-ray. If a daily rise of temperature is detected, several weeks of complete rest should be advised. It is necessary for the patient to live out-of-doors in the open air and to take carefully regulated sun baths. The strain imposed by school work and play must be avoided. Rest, adequate sleep, good food, and suitable exercise are indispensable. The repeated exposure in school to respiratory infections may prove a serious handicap in overcoming the disease.

During adolescence particular watchfulness is necessary, for it is at this age that old infections may become active and new infections be acquired. At the beginning of puberty the mortality and morbidity rates rise to the high level which persists throughout adult life. The appearance of any slight symptoms suggestive of tuberculosis should, therefore, be considered adequate reason for thorough physical and *x*-ray examination. The significance of undue fatiguability, loss of weight, the onset of a cough, pleuritic pains, and the expectoration of blood must not be underrated. Intense nervousness, flushing of the cheeks, local sweating, headaches, and digestive disturbances ought to arouse suspicion. Poor development of the

chest is often an indication of tuberculous infection. Far too often the true importance of these manifestations is not recognized by the physician, and the first suggestion of tuberculosis is given by someone who has himself been tuberculous.

In brief, the prophylaxis of tuberculosis consists, for the most part, in:

1. Safeguarding children from contact with infected individuals.
2. Pasteurization of milk.
3. Early detection of the first infection, and careful observation of adolescents and adults after the appearance of any sign or symptom suggestive of tuberculosis.
4. Education of the general public.
5. Community co-operation in hygienic matters.
6. Improvement of living conditions, so that suitable food and houses and plenty of fresh air are available.
7. Registration of consumptives and removal of as many as possible to hospitals.
8. Strict enforcement of regulations against spitting.

GENERAL TREATMENT OF TUBERCULOSIS

The treatment of tuberculosis has so many aspects that any comparatively brief description must be in some measure unsatisfactory. A conception of the character of the measures to be employed can perhaps be best derived from a consideration, first, of the general treatment, and then of the methods of dealing with special symptoms. If treatment is to be successful the physician must have a thorough knowledge of the protean manifestations of the disease and of the principles of therapy, as well as great ingenuity and resourcefulness.

It is not so much the disease as the patient that requires care. The establishment of a proper régime, in which contentment, cheerfulness, hopefulness, and full co-operation with the physician are fundamental features, is absolutely essential. Tactful education of the patient should begin immediately, so that the course of the temperature and pulse rate may be intelligently watched. Any inclination to hypochondriasis must be rigidly prevented. Careful attention to the mode of living, especially to the details of every-day life, is much more important than any form of medication. Rest, good food, and fresh air are the most effective therapeutic agents.

Although there is evidence that many tuberculous lesions heal spontaneously, most patients with even slight infection need to live with great care for several years. The mere disappearance of symptoms is not in itself a sign of cure, and the significance of the rapid improvement which so often follows a period of rest should not be overrated.

All conditions which favor the development of tuberculosis should be remedied, if possible, without surgical intervention. Teeth and gums may require care; digestive disturbances must not be disregarded; and the eyes, which are so essential in providing entertainment during the prolonged rest, must not be fatigued. This demands careful avoidance of glare and correction of all defects. The condition of the pelvis in both men and women should be ascertained. The nose, throat, ear, and larynx may require special treatment.

Rest.—Of the countless remedies for tuberculosis, complete rest is the only one which has proved eminently successful. This means not what is generally considered rest, but *absolute quiet in bed as long as fever persists.*

Some twelve years ago the writer learned a valuable lesson from a youth of eighteen. After eight weeks in bed for advanced tuberculosis the fever abated and cough and expectoration almost ceased. The patient was told he might begin to sit up. "What do you think made me improve?" asked the patient. "Rest in bed," replied the physician. "Then why should I get up?" returned the youth. He insisted on staying in bed another eight months after all symptoms had entirely disappeared, and made a complete and lasting recovery!

Even sitting up in a chair or reclining in a chaise-longue must be regarded as exercise. Since it is undesirable for the patient to walk even as far as the toilet, a bed-pan or commode should be used. The number of visitors must be strictly limited, for conversation is tiring. No invalid should be submitted to the strain of talking with a deaf person. In order to obtain absolute rest the patient must be perfectly comfortable. When able to be out-of-doors it is most important that the extremities be kept warm. If light prevents sleep during the day, a piece of black silk may be held over the eyes. Tub-baths are not desirable while the fever persists, but two sponge-baths a week are permissible.

The writer and his colleagues first pointed out in 1916 the advantages of so-called *postural rest.* Most patients prefer to lie on the side which is least diseased, but it is best that the side most involved by the active lesion be lower for the majority of the time. This allows more complete rest in the injured lung and, consequently, favors healing. Even in normal individuals the respiration, in the recumbent side posture, is much less audible at the apex of the lung on the lower side. The preliminary increase in the diaphragmatic excursion of the lower side disappears after about half an hour or an hour, and movement then becomes less; the basal respiratory murmur, which is also at first increased by change of position, soon markedly diminishes. In some cases râles have completely gone after such postural rest; and cavities which seemed to demand treatment with artificial pneumothorax have disappeared or become insignificant. Such clear evidence of improvement often makes patients more willing to persevere in following this type of treatment. Even when the immobility at first seems unbearable, it soon ceases to give discomfort.

As postural rest should continue for many months and under certain conditions for several years, attention should be paid to all the little details which add to the general comfort. The bed should be turned so that glaring light is not annoying. Careful nursing must be assured to prevent the formation of bed-sores on the hips and ears.

In order to allow *drainage of the lungs* the patient may be instructed to lie on the more healthy side for a short period each day.

When the active disease is apical and bilateral it is sometimes desirable to place *small bags of shot* (about 3 by 4 inches) over the upper part of each side of the chest in order to change thoracic breathing to the diaphragmatic type. Thus, respiration will be carried on almost entirely in the lower lobes, and the upper part of the lungs will be placed at rest. The bags should contain only a few ounces of shot at first, but the weight may be gradually increased to about 2 pounds. It is best for the patient to lie on the back

both day and night. Sewall advocates application of a suitably constructed belt to the upper thorax.

In addition to establishing the conditions for complete physical rest, it is essential so to arrange the life of the patient that all *mental strain* and *worry* be avoided. Homesickness may be very difficult to deal with, and the temperament of the patient must be carefully considered in the selection of attendants and in the arrangement of the daily routine.

Food.—It is usually desirable for tuberculous patients to have three full meals a day, but if for any reason large meals prove distasteful, smaller amounts of food may be given at short intervals. This may also be necessary when there is occult intestinal tuberculosis. Although it is best for infected individuals to attain normal weight, the overfeeding which has for some time been advocated as curative is unjustifiable and without benefit to the patient. Milk, cream, butter, and olive oil may be added to the diet in order to increase the weight. All uncooked milk should be pasteurized. It is essential that the fluid intake be abundant.

Fresh Air and Climate.—Patients who have pulmonary tuberculosis should be kept constantly in the open air and, if possible, on porches with at least two open sides. They must be protected from storms and high winds. Fresh air has an undoubted effect on skin ventilation. Sewall states that "the skin is a peripheral sensory organ specifically concerned in maintaining the hygiene of metabolism." Part of the beneficial effect of sun bathing is undoubtedly due to the accompanying exposure to fresh air. The limbs and even the whole body may be bathed in the air except when patients are susceptible to pleurisy. Beginning with two minutes at a time, the exposure can gradually be lengthened according to the weather.

Various *climates* prove helpful in the treatment of pulmonary tuberculosis. The regions in the United States which have come to be considered most favorable for tuberculous patients are quite scattered. Ashville, North Carolina, and certain parts of the Adirondacks are the best known places at moderate altitude. Among the resorts at high altitudes are those of the Rocky Mountain plateau in Colorado, New Mexico, and Arizona. Southern California and southern Arizona provide the dry warm climate which is helpful to some patients. As physicians have come to understand more clearly the requisites of the treatment of tuberculosis, and as the establishment of sanatoria has made it more possible to obtain adequate treatment, the beneficial effect of climate has recently been unduly minimized. Although definite proof of the specific influence of climate upon tuberculosis has never been obtained, physiological studies tend to demonstrate that the time-honored belief in its effect rests upon a sound basis.

There can be little doubt of the importance of the psychological effect of a change of climate. The abundant sunshine and low humidity in the Rocky Mountain plateau permit rest in the open air to be a pleasure rather than a hardship; and the fact that patients are welcomed and not considered outcasts adds much to their content. Unless it is possible to provide all the comforts of life for a prolonged period, however, it is not advisable for patients to be moved. Good food, absolute comfort, peace of mind, and suitable medical care are far more necessary than mere change of air. Although long journeys seem to do little harm even when tuberculosis is advanced, patients should not be sent to a different part of the country as a last resort.

If it does seem desirable for an individual to be moved to a region where

the actinic rays of the sun are more powerful than at sea level, careful instructions should be given. A competent physician must be consulted immediately after arrival, and a régime of rest established. The patient should remain in bed until the physician gives permission to get up. Moderate elevations and warm dry air are desirable for individuals over fifty years of age and for those with non-tuberculous renal complications. Hemoptysis is not an indication that high altitudes are dangerous, provided the proper régime is followed. After the disease has been completely arrested return to less favorable climates is permissible if precautions are taken against relapse. Some risk is always involved, however, in the change from a warm region to a climate that is cold and stormy.

Heliotherapy.—Although little success has followed the use of heliotherapy in pulmonary tuberculosis, tubercular lesions of almost every part of the body (lymph-nodes, joints, spine, larynx, abdomen, genito-urinary tract, skin, and mucous membranes) respond to such treatment. In some cases, when there is no fever and the pulmonary lesions are neither extensive nor active, exposure to the sun is beneficial. Usually the chest should not be exposed, but in children with tuberculosis of the hilum a general sun bath is helpful. The head should always be protected. At the beginning of treatment the front and back of the body are exposed for one minute each. This "dosage" may be increased one minute every day. If there is no sun the ultraviolet rays given off by quartz lamps may be substituted.

Psychic Treatment.—The toxins of tuberculosis frequently produce a restlessness which is difficult to control—so much so that in most cases it is necessary to change the mental attitude of the patient by varying the environment and the daily routine. An individual who has led an active life requires much psychological help. Homesickness must be handled with great tact. Careful explanation of the nature of the disease and of the factors controlling recovery helps destroy the morbidity and pessimism characteristic of the early stages and of certain chronic types of the disease. *Spes phthisica* is rarely seen except during the very advanced stages.

Occupational Therapy.—In order to keep tuberculous patients content much ingenuity is required. Scrap books, nature studies, learning a foreign language, stenography, telegraphy or the radio, as well as pottery, basket-making, weaving, sewing, knitting, and similar occupations may all interest the patient during the course of treatment. As games are apt to be exciting and exhausting, they should be avoided.

Exercise.—After the temperature has remained normal for several months, exercise should begin by degrees. Part of the day may be spent in a chaise-longue or reclining chair; and then very gradually the patient may begin to walk. One minute is long enough at first, but the time may be increased about a minute every third day. Walking is by far the most suitable type of exercise for individuals with pulmonary tuberculosis, and, until several miles a day produce no fatigue and no recurrence of symptoms, it should be the only form allowed. After it is safe to walk for ten minutes, motoring on good roads is a gentle and enjoyable form of exercise which is permissible.

Throughout this period of convalescence the temperature and pulse rate must be carefully watched. If exercise produces a rise in temperature, the patient must return to bed until the fever has been absent for a week. The pulse rate, which is increased by exercise, should return to normal after a few minutes of rest.

Medicinal Treatment.—There is no specific medicine for tuberculosis, nor any remedy which directly aids the tissues to combat the action of *tubercle bacilli*. Creosote and guaiacol, which have been extensively administered, may be of occasional value in reducing the amount of sputum, but do not possess curative properties. Iron and arsenic have been found of some use in decreasing the anemia and in promoting appetite and a sense of well-being. A palatable preparation of cod-liver oil has been advocated, especially for children.

Few drugs are employed in sanatoria, and the present generation of patients rarely needs "placebos."

Tuberculin Treatment.—In 1891 Koch, as the result of his observation of the so-called "Koch's phenomenon," introduced tuberculin as a specific for tuberculosis. When tuberculin was first administered the doses were so large that they produced strong reactions, but the danger of such therapy was soon realized and the dosage reduced. Although some patients doubtless recovered after these reactions, in the majority of cases they were followed by distinct aggravation of symptoms. The lesions were extended, hemoptysis occurred, and occasionally a fatal spontaneous pneumothorax was induced. Even when the doses are very small, serious results sometimes follow; consequently, great caution is necessary in the administration of this substance. Only physicians who are specially trained should inject it into a patient. Tuberculin must never be given during fever, and seems to be valuable only in treatment of the afebrile chronic type of tuberculosis. Few physicians now advocate its use. Opinion as to the relative value of the different preparations differs very much.

Autogenous Vaccines.—The inoculation of autogenous vaccine prepared from the patient's sputum seems to reduce the amount of expectoration in some cases, though it is not certain that the specificity of the organisms determines the degree of benefit derived. Autogenous vaccines must not be administered during fever. They may produce slight reactions similar to those which follow injection of tuberculin.

Artificial Pneumothorax.—During recent years artificial pneumothorax has achieved considerable popularity in the treatment of selected cases. Sterile nitrogen or air is introduced into the pleural cavity, with the intention of causing collapse of the diseased lung. The reason for the use of artificial pneumothorax in the treatment of pulmonary tuberculosis is the fact that the affected lung, as well as other parts of the body, needs rest. This has been realized for many years, but it was not until about 1908, when Saugman devised a new apparatus containing a manometer, that this type of treatment became safe. Although advisable in only a small number of cases, it sometimes produces striking results, and gives comfort and a reasonable degree of health where the condition has seemed hopeless. It should not be employed during the early stages of the disease or when more than one-third of the healthier lung shows signs of consolidation or cavity. Slight lesions in the other lung often improve if the treatment is given slowly and the patient kept completely at rest. Advanced laryngeal and intestinal tuberculosis certainly decrease the probability of ultimate success, but should not prevent this type of therapy. Since the discovery of insulin, diabetes is not a contraindication. Marked cardiovascular or renal disease renders pneumothorax of little value. The procedure should be employed whenever persistent, progressive, unilateral disease does not improve

after a reasonable period of rest, both postural and general. Violent or prolonged and repeated hemoptysis sometimes demands the prompt induction of pneumothorax. Relief usually follows immediately.

Technic.—Although absolute asepsis is essential in the operation for artificial pneumothorax, the technic may be very simple and not surgically formidable. The most favorable point at which to introduce the gas is in the fourth or fifth costal interspace in the anterior axillary line. Novocain and adrenalin are employed as the local anesthetics which should be injected into the skin with a fine needle. The pleura should be approached slowly and anesthetized carefully. In administering the gas, the oscillations of the manometer must be closely watched throughout the operation. In spite of the fact that for each individual the optimum air pressure is different, it may be said that about 300 c.c. of air should be introduced every few days. The interval between treatments may be increased one day after each administration. In the early stages of collapse the use of high pressure is always dangerous, and seldom proves more efficacious than moderate pressure. In children the first induction of air may be best carried out during anesthesia with laughing gas.

There is no evidence that nitrogen has a more beneficial effect than air, and consequently it has become customary to introduce atmospheric air which has passed through sterile cotton filters.

Most accidents are avoidable, and result from haste, lack of skill, and insufficient attention to the movements of the manometer. A large blood-vessel, a bronchus, or a cavity may be punctured. Puncturing of the lung may produce a traumatic pneumothorax. Occasionally rupture of the lung at a weak point may cause spontaneous pneumothorax, which is likely to be complicated by empyema. Collapse, as the result of pleural shock or air embolism, is very rare. An escape of air into the subcutaneous tissues is especially apt to follow the use of large needles or failure to keep firm pressure for some minutes over the needle wound after induction. Mediastinal or peritoneal emphysema rarely occurs.

Certain complications may be an obstacle to successful treatment. Pleural adhesions if not too extensive may be stretched so that they do not prevent complete collapse. They are the most common complication. Pleurisy with the effusion of a clear serous fluid eventually develops in most cases. Unless the effusion is so great as to produce symptoms of pressure it should be disregarded. The serous fluid may become purulent, and yet contain *tubercle bacilli* only. Usually it should be removed. The most serious complication is infection, either from without, which is rare, or from within, as a result of the tearing of adhesions or puncture of the lung. The formation of pus containing *Streptococci* or other pyogenic organisms is very serious. The purulent material must be frequently aspirated and the pleural cavity gently washed with weak alcohol. The action of other disinfectants, especially mercurochrome and gentian violet, is still being tested. In general, resection of a rib is necessary, and when the patient has made some improvement, surgical collapse in stage operations may result in complete cure.

The results of artificial pneumothorax depend on the advisability of the operation, the degree of collapse which it produces, and the length of time during which the collapse and consequent resting of the lung are allowed to continue. If collapse is maintained for less than two years, relapse is frequent. A number of patients in whom artificial pneumothorax was indicated and attempted, but in whom no lung collapse was obtained, have recovered satisfactorily.

The technic of collapse of one side of the chest by rib resections, in stage operations, has been gradually perfected by highly skilled surgeons. A few patients, in whom artificial pneumothorax fails, can be carefully selected to undergo this severe surgical ordeal. The final results in many instances have been most gratifying, especially if the first to the eleventh ribs, inclusively, have been cautiously resected.

Gerald B. Webb.

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LEPROSY

Definition.—Leprosy is a chronic, infectious, and contagious disease caused by the *Bacillus leprœ*. It presents a great variety of signs and symptoms owing to its tendency to implicate different tissues of the body; and usually results in death, either directly or indirectly, as the result of grave complications.

History.—There is evidence that leprosy occurred as long as two thousand years before the beginning of the Christian era. Several references to the disease are made in the Old Testament. It was common in Europe between the second and seventh centuries. In the eleventh and twelfth centuries a great epidemic began which devastated the populations of England and the continent, lasted for several centuries, and gradually subsided during the sixteenth century. In parts of the Orient (Egypt, India, China) it probably existed several thousand years ago. In Europe the segregation of the victims of the disease in leprosariums led to a gradual local wiping out of the scourge, so that at present the disease occurs only endemically and sporadically in different regions, chiefly in Iceland, Scandinavia, Russia, northeastern Germany, Galicia, Hungary, the Balkan Peninsula, Spain, Portugual, Southern France, Greece, Italy, Turkey, and parts of South America.

Incidence.—Very few parts of the world are today entirely free from the disease. Leprosy is common in China, Japan, the Philippines, the East Indies, Malaysia, Australia, India, Turkestan, Arabia, and many other parts of Asia. It is frequently encountered in Egypt, northern and southern Africa, and many other coastal countries of that continent. In the Western Hemisphere it is most common in the Hawaiian Islands, Mexico and Central America, the West Indies, the northern countries of South America, and in Paraguay. In the United States foci have existed for many years in Louisiana, Minnesota, and South Carolina. Sporadic cases are not infrequently seen in the larger cities of the Atlantic and Pacific seaboard because of immigration from countries mentioned above. A few foci exist also in Canada.

Etiology.—Leprosy is produced by the *Bacillus leprœ*, which was discovered in 1873 by Hansen. The mode of invasion of this organism is not definitely known, but a considerable amount of evidence points to a probable transmission by inhalation. In many lepers the nasal septum seems to be the first site of attack. The mucosa of the gastro-intestinal tract might be the path of contagion. Some investigators believe that certain insects, such as the bedbug, mosquito, fly, itch-mite, etc., play the rôle of intermediary host, but this has not been confirmed. That the disease is contagious there is no doubt, but it is not readily contagious, and can be transmitted from one person to another only after long-continued and intimate contact. Predisposing factors—bad hygiene, filthy environment, and unsanitary habits of living—are usually found to play a rôle in the transmission of the malady.

Leprosy is most common in individuals between twenty and fifty years of age, but it often attacks children. It is very rarely seen in infants. The disease is much more often encountered in the male than in the female. It is not hereditary and an inherited predisposition to it has never been demonstrated. Much research work will be necessary to arrive at definite conclusions with respect to modes of transmission, sites of inoculation, the rôle of insects as intermediary hosts of the bacillus, the susceptibility of exposed persons, and many other phases of the etiology of the disease.

Morbid Anatomy.—Leprosy is a neoplastic disease included in the group known as infective granulomas. The new growth produced by the causative organism, the *Bacillus leprœ*, is a granuloma composed of connective-tissue cells, epithelioid cells, vacuolated giant-cells, together with mast cells, lymphocytes, and plasma cells. Scattered through this infiltrate are variable numbers of large, ovoid cells, the so-called *lepra cells*, the exact nature of which has not been definitely determined.

The bacillus of leprosy closely resembles that of tuberculosis, both in respect to its morphology and its reactions to stains. It is from 5 to 6 micra in length and frequently presents a beaded appearance; sections of tissue often reveal enormous masses and clumps of bacilli; the organisms also occur in the lepra cells, in the walls of blood-vessels, and in the sheaths of nerves. In the cutaneous nodules of leprosy, in discharges from ulcers and from the mucosa of the nose and pharynx large numbers of organisms are frequently found. When the disease is advanced, bacilli may be found in all the viscera, particularly in the liver and spleen. Cultures of the organism on artificial media have been grown successfully by Duval, Clegg, Currie, Wellman, Hollmann, and others. Duval, among others, recently succeeded in inoculating animals with the disease. Honeij found the organism in the blood of 9 out of 28 lepers.

The histopathological picture of sections from leprous tissue often closely simulates that of syphilis and of tuberculosis; when bacteriological identification of the causative organism fails, differentiation of these diseases by means of microscopical examination of tissue is often a difficult task.

Symptoms.—Leprosy is characterized by a great variety of symptoms, partly because of the fact that different tisues of the body are concurrently affected, and partly because of the appearance of secondary lesions as complications.

The *period of incubation* is extremely variable: it may be several months or perhaps twenty or thirty years. In one of the writer's patients it was estimated to be twenty-three years.

The *pre-eruptive manifestations* are those common to other infectious diseases, and consist of backache, pains in the muscles and joints, digestive disturbances, neuralgias, and headaches. *Rhinitis* is a common prodromal symptom. Sometimes there are attacks of fever simulating malaria. Occasionally prodromal symptoms are lacking or the nervous system is chiefly implicated, and there may be attacks of pruritus, hyperesthesia, anesthesia, and various disturbances of sensation.

According to the main point of attack of the invading organisms—the skin or the nervous system—the disease assumes two clinical forms—nodular leprosy and maculo-anesthetic leprosy. A third variety, mixed leprosy, presents the symptoms of both varieties, one merging with the other.

Nodular Leprosy (*Lepra Tuberosa*).—Nodular leprosy is characterized

by the formation of nodules or lumps in the skin. These lesions are usually preceded by reddish and brownish-red spots which vary in size from $\frac{1}{4}$ inch to several inches; they may be flat or slightly elevated; the surface is smooth and frequently has a peculiar velvety texture. These develop most commonly on the backs of the hands and feet and on the face. Some spots gradually fade without leaving a trace, others slowly increase in size until they finally become elevated and nodular. Usually they appear in crops. In the larger lesions the circular central portion sometimes becomes white and depigmented. As the malady progresses nodular infiltrations and thickenings of the skin appear on the forehead, in the region of the eyebrows, in the lobes of the ears and on the cheeks, nose, and mouth, producing the so-called "leonine" expression. The outer portions of the eyebrows are lost. The hair of the scalp remains unaffected. These erythematous and nodular lesions may eventually attack any portion of the skin, so that large surfaces become involved. The fresh lesions are usually pink, red, or violaceous in color; the older lesions turn dark brown. At times there is a distinct widening of the mouths of the hair-follicles on the surface of the nodules. The entire skin may present a peculiar dusky, unhealthy hue; the forearms and legs assume a dry, scaly appearance like ichthyosis, which is especially marked in patients with dark skins. The nails frequently present small nodular infiltrations at their bases, and are at times striated and distorted. There is usually a well-marked adenitis. In some cases the legs swell, as in elephantiasis. While some of the nodules remain unaltered for long periods, others soon ulcerate, often as the result of injuries. Spontaneous healing of ulcers and absorption of unbroken nodules may take place. In advanced cases severe ulcerations go on to necrosis of the deeper tissues, which results in loss of the fingers and toes (*lepra mutilans*). Many of the lesions leave depigmented scars.

Small nodular lesions frequently develop on the mucous membrane of the pharynx, nose, larynx, conjunctivæ, and less often on the tongue. In some of these a softening and breaking down produces ulcerations, contractures, and scars. The voice becomes hoarse. The conjunctival lesions lead to keratitis, scleritis and iritis, and often to blindness. Perforation of the nasal septum is not uncommon.

The course of nodular leprosy is usually protracted; it may last from ten to twenty years or even longer. Most patients die of complications resulting from intercurrent affections, such as tuberculosis, pneumonia, bronchitis, nephritis, etc.; in others death is caused by malnutrition, exhaustion, and toxemia. In rare instances the superficial evidences of the disease regress spontaneously, and an apparent recovery takes place.

Maculo-anesthetic Leprosy (*Lepra Nervorum*).—Maculo-anesthetic leprosy is characterized by macular lesions and large flat patches, and by disease of the nerves. Prodromal symptoms are often absent, or pass unnoticed by the patient, and are usually less evident than in the nodular type. Usually beginning on the extensor surfaces of the extremities and on the back, round, oval, and gyrate macules and plaques appear, distributed more or less symmetrically on both sides of the body. Their edges are sometimes well defined, at other times they merge imperceptibly with the normal skin. The color of the lesions varies from red to violaceous or brown. Rings and irregular polycyclic figures are formed, the edges reddish-brown, the interiors yellowish or dull white in tint. The surface is smooth and free

of scales. Sometimes acute erythematous patches appear which are ephemeral and simulate *erythema multiforme*. In exceptional instances the earliest cutaneous lesion consists of a group of bullæ which later become severe ulcers.

The affected areas of skin are at first hyperesthetic and pruritic, but as the malady progresses they become anesthetic because of implication of the nerve trunks. The superficial nerve trunks, such as the ulnar, tibial, peroneal, and postcervical, become thickened and present fusiform swellings, which may often be readily palpated. This invasion of the nerve trunks and their branches results in loss of sensibility to touch, heat, and cold. As time goes on complete anesthesia supervenes. Traumatisms and burns occur without the patient's knowledge; these ulcerate and suppurate, and often result in frightful deformities. Trophic changes occur in various groups of muscles, the interossei, thenar, and hypothenar eminences frequently being first affected. Contractures of the tendons then ensue and produce the characteristic "claw hand" or "leper claw." Atrophy of the facial muscles gives the features a mask-like appearance. Perforating ulcers of the soles of the feet are common. In advanced cases there may be extensive mutilations.

This variety of leprosy is more insidious and more protracted than nodular leprosy. Death often results from complications involving the liver and kidneys, or from malnutrition and exhaustion.

Mixed Type.—Combinations of the symptoms of nodular and maculoanesthetic leprosy are frequently encountered, and constitute the syndrome of the so-called "mixed type." The predominating lesions are usually of the nodular type in the earlier stages, but later assume the symptoms characteristic of nerve involvement.

Diagnosis.—An advanced case of leprosy cannot be mistaken for other diseases, but in the prodromal stages diagnosis is attended by great difficulties. The patient, especially if he comes from a region where the disease is endemic, should be stripped and examined in a good light. Mottling and yellowish-brown discolorations of the skin, associated with areas of hyperesthesia, anesthesia, and paresthesia, should excite suspicion. The following changes should be carefuly looked for: thickening of superficial nerve trunks; thickening of the ear lobes and supra-orbicular regions; loss of eyebrows; nodules and deformities of the nails; atrophy of the muscles; and nasal, pharyngeal, and laryngeal lesions. The earlier, erythematous patches sometimes resemble *erythema multiforme*, but are of longer duration; there is no sensation of burning or smarting; on the contrary, the lesions are often anesthetic. Nodular leprosy sometimes simulates *syphilis*, but the duration of the syphilitic eruption is much shorter. The history of a primary lesion and secondary eruptions, together with evanescent lesions of the buccal mucosæ, should be taken into consideration; hyperesthesia, anesthesia, and paresthesia are lacking. The *Wassermann reaction* is frequently positive in non-syphilitic lepers affected with nodular leprosy. A recently published modification of the test perfected by Kolmer seems destined to become of practical use in the laboratory differentiation of the two diseases. The *bacteriological diagnosis* is, of course, the scientific method of differentiation; in leprosy, smear preparations should be made from the nasal and buccal secretions, from the surface of ulcers and excoriations, and even from the serum of a curetted papule, in an attempt to find the

specific bacilli. In patients with suspected syphilis search should be made for the *Spirochæta pallida* in the secretions of moist lesions, the serum of curetted papules, or in the fluid of aspirated lymph-nodes. The result of the Wassermann test is significant. In both diseases microscopical examination of sections of tissue are often decisive. The therapeutic test in syphilis is of great value.

Certain manifestations of *lupus vulgaris*, of *mycosis fungoides*, of the *hemorrhagic sarcoma* of Kaposi, of *vitiligo*, of the comparatively rare *annular syphilids*, and of a few other eruptions characterized by rings, gyrate and polycyclic figures are sometimes apt to cause confusion in differential diagnosis; but in the great majority of instances in which these diseases might obtrude themselves the actual diagnostic difficulties encountered are more imaginary than real.

During *syringomyelia*, which is apt to be confounded with leprosy, there is an alteration of the pain and temperature sense without loss of tactile sensibility—the so-called "dissociated anesthesia"; the occurrence of painless whitlow and various trophic disturbances in the absence of cutaneous manifestations is evidence of this disease and not of leprosy.

Prognosis.—Until the last few years the outlook for the leper has always and everywhere been regarded as hopeless. Despite the fact that some patients with spontaneous regression of symptoms and temporary freedom from lesions have been encountered, the overwhelming proportion die wretchedly. Recent investigations of the chemotherapeutic properties of the ethyl esters of chaulmoogra oil have, however, changed the prognosis from "very bad" to "hopeful." Reports of cures are now appearing in the literature.

Patients suffering from the less virulent maculo-anesthetic variety are apt to live for one or more decades in comparative comfort, depending upon environment, nursing, hygiene, etc. The prognosis of the nodular and mixed varieties is far less favorable.

Treatment.—Like tuberculous patients, lepers are apt to contaminate their immediate surroundings with secretions and excretions. Coughing, sneezing, and spitting presumably play an important part in the dissemination of the disease; the urine and feces also harbor bacilli. Patients with "open" lesions—excoriations, ulcers, secreting wounds, etc., both of the skin and mucosæ—should be strictly segregated. The United States Government maintains leprosaria in Louisiana and California. Large cities provide housing and facilities for the segregation of lepers. Patients with the maculo-anesthetic variety, especially when they have no demonstrable excoriated lesions in the nasal, buccal, or pharyngeal mucosæ, need not generally be strictly segregated, but they should be required to take all precautions against contamination of others. Long-continued association with the non-leprous must be avoided; rooms, bedding, wearing apparel, cooking utensils, etc., must be used only by the patient, all precautions being carried out just as in pulmonary tuberculosis.

Many remedies have been used, nearly all of them unsuccessfully, with one exception, namely, *chaulmoogra oil* and its derivatives.

Pure chaulmoogra oil may be administered *per os*, in doses of from 5 to 60 drops, three times daily; it may be taken with a lump of sugar or mixed with milk or Vichy water. Some patients bear it well; in others it causes gastritis which necessitates cessation of the medication. Many patients

have, however, improved strikingly after long-continued ingestion of this oil.

The modern treatment, and the most efficacious, consists in subcutaneous and intramuscular injections. *Mercado's formula,* which was extensively employed by Heiser with very good results, is as follows:

Chaulmoogra oil	60 c.c.
Camphorated oil	60 c.c.
Resorcin	4 gm.

From 5 to 60 drops or even more of this mixture are injected into the gluteal muscles two or three times per week. This often gives rise to considerable pain at the site of injection. Currie and Hollmann claim to have had better results with

Iodin	1 gm.
Oil of eucalyptus	8 c.c.
Camphor	2 gm.
Olive oil	147 c.c.
Chaulmoogra oil	150 c.c.

mixed in the order given, using heat. The maximum dose is 10 c.c., given intramuscularly, once a week.

Apparently the most promising results thus far obtained have been from the use of the *fatty acids of chaulmoogra oil;* Hollmann and Dean, in the course of their investigations in the Hawaiian Islands, have for some years been administering the ethyl ester of the fatty acids of the oil, with very promising results. A large proportion of their patients have been helped, and a considerable number apparently cured—that is, cured in the sense that lesions became undemonstrable and bacillary findings negative. This product is on the market and may be obtained in large cities. It is injected into the gluteal muscles twice a week, in doses ranging from 10 drops to 1 dram. Treatment must be continued over prolonged periods—two, three, even five years—with intervening periods of rest.

As in syphilis and tuberculosis, the earlier in the course of the malady that treatment is instituted, the more helpful will be the outlook for the patient.

Cutaneous lesions—plaques, nodular infiltrations, and ulcerations—often respond favorably to exposure to the Roentgen ray. Infiltrated lesions and deep-seated ulcers should be treated with filtered rays (the average dose being 1 Holzknecht unit, skin distance, filtered through 3 mm. of aluminum screen) once every three or four weeks. Radium should be employed for lesions in the mouth and about the eye. Antiseptic and general surgical procedures are necessary in advanced cases. Frequent hot baths with sodium bicarbonate dissolved in the water are beneficial. Change of climate and the use of a good tonic, such as a combination of iron, quinin, and strychnin, are at times helpful.

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GLANDERS

(*Malleus, Farcy, Glanders of the Skin*)

Definition.—Glanders is an acute or chronic infectious disease of horses, asses, and mules, which occasionally is communicated to man. It is characterized by the formation of small nodules in the skin or mucous membranes that tend to ulcerate.

Distribution and Incidence.—The disease has been reported in cats, rabbits, sheep, guinea-pigs, field mice, and several of the wild animals, especially those of the cat tribe. Swine and pigeons, on the other hand, are only slightly susceptible, and cattle, white mice, and domestic fowls are immune. The disease exists in many parts of the civilized world, but is commonest in those parts where traffic in horses is active. In New York City, for example, where, as in many other localities, the horse has been largely eliminated, glanders is now an almost unknown disease. During a recent period of twenty years 7 cases of glanders were admitted to the wards of Bellevue Hospital; in the past eight years, however, not a single case has been seen. In man cutaneous glanders, or the so-called farcy, is the commoner form.

Bacteriology.—The causative micro-organism, namely, *Bacillus mallei*, is a small rod with rounded ends, varying from 3 to 4 micromillimeters in length and from 0.5 to 0.75 in breadth. The rods are usually straight, occasionally slightly curved. The bacillus is non-motile and does not form spores. It stains easily with the usual aniline dyes, but is readily decolorized. The best results are obtained by warm methylene-blue. The micro-organism shows distinct irregularities in its staining qualities, granular, deeply colored areas alternating with faintly stained or unstained portions. This characteristic is helpful from the diagnostic standpoint. The micro-organism is easily grown on most culture-media, but its most characteristic appearances develop when implanted on potato, where, within forty-eight hours, the surface becomes covered with a yellowish, transparent, slimy layer, which gradually grows darker until it assumes a deep reddish-brown hue. In employing this cultural characteristic for diagnostic purposes, however, it must be remembered that similar appearances are produced on potato by the growth of Bacillus pyocyaneus. The bacteriological diagnosis of glanders may be made by isolating and identifying the bacilli from the broken-down glanders nodule. At the same time material from the nodule should be injected into the peritoneal cavity of a male guinea-pig. At the end of twenty-four or thirty-six hours the guinea-pig's testicles will have become markedly swollen, and section reveals intense purulent inflammation.

The glanders bacillus may be readily obtained from the pus, both by smear and culture. This diagnostic procedure was introduced by Strauss and is known by his name. Similar changes in the testicle, however, have been observed by Hallopian and Bureau following the inoculation of pus from a case of human mycosis into the peritoneal cavity of guinea-pigs. In the same way Nocard has described a slightly contagious farcy-like lymphangitis in horses, due to a micro-organism which likewise produces orchitis when inoculated into male guinea-pigs, the micro-organism differing, however, from Bacillus mallei in its cultural and staining characteristics. Similar changes in the testicle of the guinea-pig follow the inoculation of material from the so-called coccidioidal granuloma. Nevertheless, in spite of the fact that orchitic changes may be produced as a result of the inoculation of various types of diseased tissue, the Strauss test in glanders occupies a place of great diagnostic value.

Symptoms of Acute Glanders.—The period of incubation may be short, three to five days, or it may be prolonged to one or two weeks or even more, one of the Bellevue cases having started between three and four weeks after inoculation. The diagnosis in man is sometimes extremely difficult, especially if there is no history to guide the physician and if the patient's occupation be not known. The mode of onset varies. In one group of cases the disease is initiated by malaise, nausea, headache, vomiting, pain and tenderness in different parts of the body, shivering and chilly sensations, with elevation of temperature, which may be subcontinuous, intermittent, or remittent. These symptoms are followed in time by the appearance of abscesses in the skin, accompanied by intense local reaction, particularly along the line of the lymphatics, where nodular subcutaneous enlargements, the so-called farcy buds, appear and rapidly succumb to ulceration, or by an eruption of abscesses in the mucous membrane of the nose that ulcerate and release a profuse sticky discharge, sometimes associated with similar changes in the larynx and lungs. In other instances the disease starts with the symptoms of croupous pneumonia, one of the Bellevue patients, for example, having been stricken suddenly with chills, elevation of temperature, cough, dyspnea, and severe pleuritic pains, the latter due to abscesses in the pleura. Or the disease may commence with the general symptoms already referred to, and these may become associated with acute joint changes, the picture, as a whole, suggesting acute rheumatic arthritis. In other instances the disease commences with symptoms indicative of typhoid fever or acute miliary tuberculosis. In 2 of the Bellevue cases the patients first complained of prostration, headache, nausea, diarrhea, and cough. In still other cases the general symptoms of sepsis, as already outlined, are followed by the appearance of multiple abscesses in the skin of the chest or abdomen, frequently associated with an eruption of pustules in the region of acutely inflamed joints; or the pustular eruption may become generalized and the disease be mistaken for smallpox. The occurrence, however, of symptoms of an acute infective disease in an individual who comes in contact with horses and who presents multiple abscesses in the skin or in the mucous membrane of the nose, with deep-seated pain or tenderness, indicative of abscesses in muscle tissues, tendon sheaths, fascia or periosteum, with or without joint symptoms, should suggest the diagnosis of glanders in spite of the extreme rarity of the disease, and confirmation should be sought in isolation of the causative bacillus and guinea-pig inoculation.

Symptoms of Chronic Glanders.—Chronic glanders starts insidiously and is rarely attended by other than negligible constitutional symptoms. It is characterized by the development of localized nodular formations in the skin and elsewhere that break down and form sluggish ulcers, the latter discharging viscid pus which contains characteristic bacilli, usually, however, in small numbers. In rare instances the glanders abscess is solitary. For example, in a stable-boy who came under my observation at the New York Hospital, a solitary abscess appeared in the right forearm. Pus was aspirated, and an injected guinea-pig came down in the next thirty-six hours with typical testicular lesions in which Bacillus mallei were demonstrated by smear and culture. Excision was followed by apparent recovery. In connection with the latter point, however, it is to be observed that a striking feature of the chronic disease consists in alternation in the processes of destruction and healing. Abscesses, when they break spontaneously or are incised, may heal, only to erupt locally or at a distance after an interval of weeks or months, and examples sometimes are encountered in which the disease remains latent for years. Cases of so-called cured chronic glanders are recorded, but, in view of this tendency of the process occasionally to remain latent for a long period, all "cured" lesions should be regarded with suspicion. Exacerbations are prone to occur and death may result from acute glanders. In chronic glanders in man, ulcerative lesions in the mucous membrane of the nose occasionally occur, giving rise to persistent discharge of sticky excretions. This condition resembles an ordinary chronic nasal catarrh, and, for this reason, the nature of the disease is sometimes entirely overlooked.

Diagnosis.—In arriving at a diagnosis of glanders the occupation of the patient is of prime importance, and any individual who comes in contact with horses should be suspected of glanders whenever he presents the symptoms of an otherwise unexplained infective process. In these circumstances search should be made for the presence of abscesses in the skin, mucous membrane of the nose, larynx, muscle tissues, periosteum, etc. In the same way, any individual who comes intimately in contact with horses and who does not complain of constitutional disturbances of any moment, but presents signs of persistent solitary or multiple cutaneous or mucosal abscesses, should likewise be suspected of glanders. Once this suspicion is entertained, the contents of the abscess should, first, be stained in hot methylene-blue solution and examined for the bacillus of glanders; second, the pus should be cultivated, preferably on potato; third, pus should be inoculated into the peritoneal cavity of a male guinea-pig, when, if glanders be present, the pig, at the end of twenty-four or thirty-six hours, will present marked swelling of the testicles, and the testicle, on section, will reveal wide-spread purulent infiltration from which the glanders bacillus may be recovered in smear and culture (Strauss's test).

Prognosis.—Recovery from acute glanders is highly problematic, and in all such cases the gravest prognosis is to be predicated. In chronic glanders, on the other hand, the outlook is hopeful, particularly if the abscesses are accessible and can be excised or incised and drained.

Prevention.—Practically every glanders animal is a spreader of the disease and should be promptly destroyed, the stables thoroughly disinfected, including harness and watering bucket. Animals that have been exposed to infection should be tested for glanders. Those that respond should, accord-

ing to one opinion, be destroyed; other authorities affirm that if the reacting animals are segregated, worked together in pairs or singly, and are watered from individual buckets, it is safe to keep and use them until symptoms of glanders develop, when they should be promptly destroyed. This opinion is based on the fact that many horses giving a reaction to specific tests for glanders eventually recover (Moore). Other causes for the spread of glanders are the common water-trough, the interchange of feed-bags, and the like.

Treatment.—The treatment of acute glanders is purely symptomatic. The chronic form demands surgical intervention—excision or incision.

DOUGLAS SYMMERS.

ANTHRAX

(Woolsorters' Disease, Pulmonary Anthrax, Malignant Pustule, Cutaneous Anthrax, Charbon, Milzbrand)

Definition.—An acute infectious disease of herbivora, caused by the *Bacillus anthracis* and transmissible to human beings, in whom it occurs in three forms, namely, cutaneous, pulmonary, and intestinal.

Distribution and Incidence.—Zoölogically and geographically anthrax is the most wide-spread of all infections. Practically all warm-blooded animals are vulnerable. It is largely, however, a disease of herbivora, attacking especially cattle, hogs, sheep, and goats, and among them ravishing epidemics are by no means rare, so that the economic significance of the disease is profound. In Russia, where the disease is common, 72,000 horses are said to have succumbed in a single year, and it has likewise been known to decimate herds of reindeer. Geographically it has no limitations, although, perhaps, Continental Europe has suffered more than any other expanse. In the United States it is comparatively rare. In the course of the past ten years 38 cases of cutaneous anthrax have been admitted to the isolation pavilion of Bellevue Hospital, which is one of only four institutions in New York City where anthrax patients may find sanctuary. Blanton estimates that cutaneous anthrax, which is the most common form in men, occurs in the United States to the number of about 130 cases every year. In man anthrax usually occurs in isolated instances, although in occasional circumstances it is to be seen in epidemics of limited proportions, particularly among longshoremen who have been engaged in unloading the same cargo of infested hides. Anthrax, cutaneous and otherwise, is essentially, although not exclusively, an occupational disease, occurring most frequently among those who handle hides, hairs, bristles, wool, horn, and bone, and among farm laborers, shepherds, butchers, and veterinarians. Protection of workers is particularly difficult in the leather industry, since practicable means of disinfection such as exist for hair and bristles have not yet been worked out for hides and skins. Non-occupational anthrax is most frequently traceable to inoculation from infested horse-

hair shaving brushes. Thus, of the 38 cases of anthrax observed at Bellevue Hospital, 13, or 35 per cent., were traceable to this mode of transmission. The danger from this source is furthermore indicated by the fact that Symmers and Cady found virulent anthrax bacilli in 7 per cent. of a series of cheap shaving brushes openly purchased from peddlers in the streets of New York City.

Etiology.—The exciting cause of anthrax is the *Bacillus anthracis*. Historical interest attaches to this micro-organism in that it was the first proved to bear a specific relationship to an infectious disease. Modern bacteriology, therefore, was conceived, as it were, in those researches which demonstrated the specificity of the bacillus of anthrax. The micro-organism is a straight rod, 5 to 10 micra in length and 1 to 3 in breath. It is non-motile. In artificial culture-media it forms long threads and the ends of the individual bacilli are cut off sharply, the general formation being not inaptly comparable to a rod of bamboo. In the blood and other tissues of infected animals spore formation does not occur because of the lack of free oxygen. In view of its property of spore formation, the anthrax bacillus is extremely resistant to chemical and physical agents. The bacillus is conveyed to animals sometimes by direct inoculation, as by bites and by the sting of insects, occasionally by feeding on carcasses of animals which have died of the disease, but most commonly by grazing in contaminated pastures. In man the most common method of infection is by direct inoculation of the skin, rarely by ingestion or through the lungs.

Cutaneous Anthrax.—The site of inoculation is usually on an exposed surface, most often on the face or neck, corresponding to the area covered by the shaving brush, or to local inoculation from carrying infested hides on the shoulder, occasionally on the arm or hand. The lesions on the face and neck are apt to display signs of greater severity than those on the hand or arm. The disease is initiated by intense itching at the point of inoculation; this is rapidly followed by the appearance of a small papule which soon becomes vesicular and then spreads to form a large dark brownish eschar, covering and surrounding which are numbers of minute silvery vesicles. Within a few hours after the appearance of the papule, which is painless, the soft tissues in the immediate vicinity become swollen due to the presence in them of a protective substance known as anthracomucin. In lesions on the neck the area of swelling frequently extends upward in such fashion as to cause closure of the corresponding eyelid, and downward on to the chest or even as far as the abdomen. At this time the anthrax lesion is absolutely characteristic and could scarcely be mistaken for any other condition known to cutaneous medicine. The temperature varies; on occasions it is elevated; frequently it is normal throughout and sometimes it is subnormal. While the anthrax lesion itself offers a forbidding aspect, the appearance of the patient is apt to give one the impression of extraordinary tranquillity, even though his blood may be swarming with anthrax bacilli. This complete lack of apprehension on the part of an individual suffering from a disease which is popularly invested with an intense sense of dread is an almost unfailing symptom. For example, I have seen a victim of anthrax contentedly reading a newspaper twenty minutes before death. Incidentally, it is to be remarked that the mode of action of the bacillus of anthrax in these circumstances is still an unsettled point. It is probable that death is brought about in many instances by

mechanical means, such as bacillary occlusion of the capillaries of the brain and elsewhere. Neither a true secretory toxin nor an endotoxin has been demonstrated. The toxemic nature of the disease in experimental animals, however, and occasionally in man, indicates the possibility that such poisons may exist.

Complications and Sequelæ.—As a rule, cutaneous anthrax pursues an uneventful course, terminating in death or in recovery without complications or sequelæ. There are cases, however, in which the disease becomes septicemic without signs of visceral involvement; at other times septicemia is associated with changes indicative of pulmonary or intestinal implication or endocarditis, sometimes meningitis. In other cases the infiltration of the soft tissues by anthracomucin takes place to such an extent that the skin becomes gangrenous. Finally, it is to be noted that the cutaneous lesion, when it heals, leaves a deep disfiguring scar. Those patients who have been treated with anti-anthrax serum sometimes escape serum sickness; others are afflicted in varying degrees of severity. In one of our Bellevue patients serum treatment was followed by edema of the scalp to such an extent that the patient could not wear his hat and by intense symptoms referable to the joints and stomach.

Diagnosis.—Given a large brownish or brownish-black eschar situated on an exposed surface, particularly the face or neck, surrounded and covered by silvery vesicles and set in the midst of an immense area of swelling, together with the occupation of the patient, the diagnosis of cutaneous anthrax is, as a rule, to be made at a glance. Of course, bacteriological examination should be carried out in every case both by smear and culture. The former method, as a rule, yields anthrax bacilli in considerable numbers. There are occasions, however, when the smear shows them in small numbers or even not at all. In one of the Bellevue cases the patient presented a clinically typical anthrax pustule on the under surface of the chin. Smear failed to reveal anthrax bacilli and culture showed a pure growth of Staphylococcus aureus. The shaving brush with which the man had presumably been infected yielded a growth of virulent anthrax bacilli. In all cases agar plates of the blood should be made instantly the patient comes under observation. There are several varieties of anthracoid bacilli which on plates yield colonies scarcely to be distinguished from those of genuine anthrax. In order to determine the virulence of the organisms in question guinea-pigs should be inoculated. In the case of genuine anthrax the area of inoculation at the end of twenty-four hours is hemorrhagic and infiltrated by anthracomucin; the suprarenal capsules are hemorrhagic, and typical anthrax bacilli can be recovered by smear and culture from the local lesion and from practically every organ in the body.

Pulmonary Anthrax.—This variety of anthrax is clinically negative. There is no external lesion and usually the patient feels perfectly well until a few hours before death. The respiratory symptoms are, as a rule, relatively negligible. Some of the patients complain of a feeling of tightness in or pressure on the chest and difficulty in breathing. In others breathing is accelerated, sometimes to the extent of 40 or 50 respirations to the minute. Cough is often present, but is seldom severe. The percussion note is clear and the auscultatory signs are usually those of diffuse bronchitis. The disease occurs most often in those whose occupation subjects them to the inhalation of dust from infected hairs, wool, and the like.

In the more rapidly fatal cases death occurs within eighteen or twenty hours. In other instances the disease may pursue a course extending over four or five days, and occasionally it may last nine or ten days. Rapidity is the rule, however, and in all cases the prognosis is extremely grave. Once the diagnosis is made or even when the disease is suspected, the patient should be given massive doses of anti-anthrax serum, namely, an initial dose of 150 or 200 c.c., followed by 50 or 100 c.c. every four hours.

Gastro-intestinal Anthrax.—The gastro-intestinal is the rarest form to be encountered in human beings. The symptoms, as is to be expected, are mostly abdominal and consist in nausea, persistent vomiting, abdominal pain and tenderness, and diarrhea, which frequently is hemorrhagic. The disease is apparently capable of arising as a result of ingestion of anthrax bacilli or as a secondary manifestation of anthrax in some other portion of the body, notably the skin. One of Teacher's patients was a lead worker, and careful inquiry eliminated all of the customarily recognized sources of infection, the evidence pointing to inoculation by swallowing. Butler and Huber have recorded an outbreak of 25 cases occurring in a group of individuals who had partaken of the flesh of an anthrax-infected animal. The only case of gastro-intestinal anthrax to be encountered at Bellevue Hospital was that of a young girl who gave a history of having recently purchased and worn a cheap fur neck-piece. She was admitted to the hospital with an anthrax pustule in the skin of the upper part of the chest and died a few hours later. At autopsy the intestines revealed multiple hemorrhagic and necrotic ulcerated areas attended by marked injection of the blood-vessels in the corresponding serosa, microscopical examination showing bacillary thrombosis.

Prognosis.—The prognosis in cutaneous anthrax is to be gauged largely by the length of time that has elapsed between the appearance of the pustule and the institution of treatment, and by the degree of meddlesome interference, if any, that has been practised during this interval. Frequently the anthrax pustule is not correctly diagnosed, partly because comparatively few physicians have had an opportunity to observe the disease and partly because the patient, feeling in full possession of health, avoids medical advice until the pustule has reached such an extent as to cause disfigurement or local annoyance. If in the interim the pustule has been subjected to the action of physical or chemical irritants, the possible existence of septicemia must be borne in mind. Such a development, of course, renders the prognosis highly dubious. If, on the other hand, the pustule be unmolested from the outset, and if the patient comes under observation before the end of the third day, the prognosis is favorable. After the third day the possibility of septicemia increases, especially in ambulant cases. In a word, if the pustule be recognized early, and if the patient be placed at rest in bed, and if no local interference be practised, the chances of recovery are in the patient's favor, and, even if septicemia develops, there is a possibility of cure if anti-anthrax serum be given intravenously in massive doses. Certain it is that cutaneous anthrax is not so deadly as to merit the wholesome fear with which the mere mention of the name "anthrax" is popularly associated. Pulmonary and gastro-intestinal anthrax, on the contrary, are almost invariably septicemic, and the prognosis is grave partly for this reason and partly because of the presence of destructive changes in the lungs and intestines, respectively, although here,

again, hope is not necessarily to be abandoned if anti-anthrax serum be administered promptly and in abundance.

Treatment.—The experience of recent years indicates that we must relinquish certain conceptions which have been bequeathed to us concerning the therapy of anthrax in man. It is now known, for example, that the pustule of cutaneous anthrax may heal spontaneously if left to its own devices, and that, if subjected to operation, cauterization, or other such forms of local treatment, septicemia may be precipitated. Our experience at Bellevue Hospital has led us to believe that every anthrax lesion of the skin or elsewhere should be tentatively regarded as attended by generalized infection until the result of the blood-culture proves the contrary. In such circumstances the patient should be placed at rest in bed. If no serum is available the lesion should be covered with a bit of sterile gauze to collect the secretions, but otherwise left absolutely alone. If, however, anti-anthrax serum is to be had, the patient should receive at once an intravenous dose of 150 to 200 c.c. of serum, warmed to the temperature of the blood, supplemented by 40 c.c. every four hours for at least twenty-four hours, preferably forty-eight hours, since, in occasional cases, blood-cultures require this length of time for the bacillary colonies to develop. In anthrax septicemia, which is commonly regarded as a form of infection that is practically always fatal, this method of treatment should be continued until the blood-cultures are sterile or until death supervenes. That anthrax septicemia is by no means invariably fatal is shown by the fact that the literature of recent years contains references to 7 cases in which recovery occurred. An eighth and unpublished case of anthrax septicemia has since been successfully treated at Bellevue Hospital. Although I have had no experience with the employment of anti-anthrax serum in the pulmonary and intestinal forms, it seems to me that the same method of treatment is equally urgently indicated.

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PLAGUE

Definition.—Plague is primarily an enzoötic or epizoötic disease of rodents caused by *Bacillus pestis*. The bubonic form is transmitted to man by fleas from infected rats.

History.—Plague has been known in the Levant for about 3000 years. Pandemics occurred in the sixth and fourteenth centuries. The second of these, known as the Black Death, originated in eastern Asia, and caused the death of one-fourth of the population of Europe. The present pandemic started in China in the province of Yünnan, spread through Canton to Hongkong, and thence to all parts of the world. In India alone it has resulted in a mortality of over 10,000,000. Recently Wu has adduced evidence that the central Asian highlands are the original home of plague and suggests that the plague bacillus is propagated continuously in one or more rodents native to this region.

Etiology and Epidemiology.—Kitasato and Yersin, working independently in Hongkong, described *Bacillus pestis* almost simultaneously in 1894. The disease is a rat infection transmitted to man only by the rat flea. Patients with bubonic plague are not a source of infection unless they develop a secondary plague pneumonia. In the intervals between epidemics the disease is propagated as a chronic rodent enzoötic. The important causes of the development of the rat epizoötic and the human epidemic which usually follows have been determined in India and the Dutch East Indies.

The rats usually infected with plague are *Mus norvegicus* and *M. rattus*. Other rodents exceptionally transmit the disease.

Fleas.—The most common transmitter of plague is *Xenopsylla cheopis*. Other fleas are capable of doing so, but play a minor part. Recently Hirst and Cragg have shown that *Xenopsylla astia*, which was previously confused with *Xenopsylla cheopis*, does not transmit plague readily from rat to rat and bites man with reluctance. The distribution of these two fleas may explain the irregular occurrence of plague in India. Although other insects, *e. g.*, the bedbug, have been shown to be capable of transmitting plague, their actual influence is negligible.

The Mechanism of Plague Infection.—*Bacillus pestis* is not found in the salivary gland of the infected flea. Until recently infection was thought to occur by rubbing the feces of an infected flea into the flea bite wound or by scratching. Bacot and Martin have shown, however, that the proventriculus of the infected flea becomes obstructed by a mass of multiplying plague bacilli and that later attempts to feed on man cause regurgitation of *Bacillus pestis* into the wound. These authors believe that this is the usual mechanism by which plague is transmitted.

Bacteriology.—*Bacillus pestis* is a pleomorphic, Gram-negative bacillus of the hemorrhagic septicemia group. It grows well at room temperature, development being optimal at 30° C. On agar it produces tiny dewdrop-like colonies in twenty-four hours which later become semitranslucent gray. It stains at the poles, especially when obtained from lesions. Its fermentation reactions resemble those of *Bacillus typhosus*, from which it is distinguished by its specific agglutination and thermoprecipitation reactions, its lack of motility, and its peculiar involution forms on salt agar and in old cultures. In bouillon with floating oil drops the characteristic stalactite growth appears in a few days.

Pathogenesis.—*Bacillus pestis* produces typical lesions and death in the ordinary laboratory rodents and in many wild ones. Monkeys and cats are also susceptible. Hemorrhagic gelatinous edema develops at the site of injection. The other changes are those of naturally infected rats. Recognition of the lesions of rodent plague, which is of greatest importance, requires experience. In acute cases there is bloody edema around the swollen lymph-glands, most often around the submaxillary; subcutaneous injection; fluid in the pleural cavities; and pinhead-sized, yellowish nodules in the enlarged fatty liver. In chronic rat plague the spleen is increased in size and contains nodules in which there are plague bacilli. The lymph-nodes are usually enlarged and caseated and are surrounded by a zone of hemorrhagic edema.

Morbid Anatomy.—Bubonic Plague.—In man the changes are essentially those found in infected rodents. On the skin vesicles, pustules, or the

so-called plague carbuncles may appear. Usually there is marked postmortem lividity, hence the name "black death." Section of the skin over the primary bubo reveals the same pathological changes observed in an experimental animal. Similar but less marked lesions (secondary buboes) are present in the more distant lymph-nodes. Frequently the organism breaks through the lymphatic defence and sets up bacteremia. The *myocardium* undergoes cloudy swelling with small hemorrhages. The *lungs* may be the site of edematous bronchopneumonia (secondary) and fibrinous pleurisy. The *spleen* is enlarged and hemorrhagic and contains bacilli. In the *liver* there is cloudy swelling or fatty degeneration and sometimes small metastatic abscesses containing *Bacillus pestis*. There are no characteristic changes in the *kidneys*, although cloudy swelling and early fatty degeneration as well as petechiæ under the capsule and in the pelvices are sometimes encountered. In the *alimentary tract* there may be ecchymoses or even hemorrhages.

Pneumonic Plague.—The pathological changes of pneumonic plague are essentially those of bubonic plague, except that there is invariably a more or less massive, edematous bronchopneumonia with fibrinous pleurisy. Usually, at least in primary plague pneumonia, the infection is of bronchial origin. The cutaneous and lymphatic manifestations of bubonic plague except for the postmortem lividity are absent. There is always bacteriemia.

Symptoms.—Bubonic Plague (*Pestis Bubonica*).—(*a*) *Pestis minor* is a mild form of bubonic plague characterized by headache, slight fever, nausea, and tenderness or pain in the affected lymph-nodes which are usually in the groin. These symptoms may disappear within two or three days or the node may suppurate. *Bacillus pestis* may be recovered from the bubo. Such cases frequently are ambulatory. Death is rare.

(*b*) *Pestis major* (*typical bubonic plague*), after an incubation period of two to five days, begins with chilly sensations, rarely with marked rigor. There is sleeplessness, headache, pains in the back and legs, nausea, and sometimes vomiting. The gait is unsteady or even staggering, as in alcoholic intoxication. The mind reacts slowly. The face is frequently dusky red and the eyes injected. The temperature varies from 102° to 105° F., and the pulse and respiration rates rise in proportion. The prostration and dulness increase and the temperature may fluctuate widely. The tongue becomes coated; the lips and teeth covered with sordes. The vomiting may persist. Constipation is usual, but diarrhea may occur. The spleen is enlarged always; the liver frequently. Symptoms of myocardial weakness are generally manifest. The leukocyte count sometimes rises to 80,000 or 90,000 per cubic millimeter. Characteristic buboes usually appear the first day, most often in the groin, less commonly in the axilla and neck. The boggy induration, which is very painful, causes the patient to lie in such a position as to relieve the tension in the swelling as much as possible. The bubo may resolve in a week or two or slowly suppurate and slough. In favorable cases the temperature begins to fall by lysis after two to five days, the skin becomes moist, the buboes less tender, and there is general improvement. Convalescence may be very protracted. Death, frequently sudden, is due to myocardial failure during exertion or to secondary hemorrhage from sloughing buboes. It may also follow a protracted illness with general weakness referable to suppuration of buboes.

Pneumonic Plague (*Pestis Pneumonica*).—In primary pneumonic

plague the infection is carried by droplets coughed out by a living plague patient, *i. e.*, by respiratory transmission from man to man. Symptoms referable to infection of the lymph-nodes through the skin are therefore lacking. Patients who develop a secondary plague pneumonia in the course of bubonic plague suffer the characteristic respiratory symptoms in addition to those of the other type of the disease. Those peculiar to plague pneumonia are the development of a cough, after an increasing sensation of constriction in the chest, which at first is dry and hacking, but within a few hours raises a watery sputum that rapidly becomes frothy, and still later assumes a pinkish color because of a uniform admixture of red blood-cells, or more rarely contains streaks of blood. Such sputum is in marked contrast with the sticky, rusty sputum of typical pneumococcus pneumonia. The increase in the proportion of blood is progressive and the plague bacilli also become more abundant. The dark reddish flush of the face and body is accentuated. Usually respiration is rapid (30–50 per minute), but there is no pleuritic pain. Dyspnea may be present. Death usually supervenes within twenty-four hours of the appearance of the characteristic sputum.

Septicemic Plague.—The term "septicemic plague" is somewhat misleading. Probably most bubonic and all pneumonic cases become septicemic (bacteremic). In both these types of plague, however, the disease may develop so rapidly that death from septicemia ensues before the characteristic signs of buboes in the one, or of bloody sputum in the other, have become manifest. Often the patient falls down and dies after displaying few or no premonitory symptoms. In other cases the onset is violent, with rigors, fever, vomiting, cardiac weakness, and marked prostration which leads to death within a few hours. To this type the name *pestis siderans* (fulminant plague) has been given. At autopsy characteristic early changes are found in widely disseminated lymph-nodes or signs of incipient plague pneumonia may be discovered. Leukopenia often occurs instead of leukocytosis.

Complications.—The most important complication of bubonic plague is plague pneumonia, which is almost uniformly fatal. Occasionally secondary infection develops from the sloughing bubo or secondary hemorrhage occurs from the large vessels which have been exposed by the destruction of tissue.

Diagnosis.—During a recognized epidemic diagnosis is not difficult; indeed, other diseases may be erroneously diagnosed and treated as plague.

Physical Examination.—If plague is suspected the examiner should wear a mask. Pneumonic patients are infectious as soon as the cough begins. The toll has been high among physicians who have contracted the disease while examining unrecognized pneumonic plague. In countries where the disease is uncommon and there is no epidemic it is unlikely that isolated cases will be diagnosed correctly, at least until the buboes have developed. Aside from the boggy induration around the inflamed lymph-nodes there is nothing strikingly peculiar. In plague pneumonia perhaps the most significant manifestation is the indefiniteness of the signs, which are those of an ill-defined lobular or bronchopneumonia that continues to spread. The respiratory sounds are suppressed or modified to definite tubular breathing. There are fine moist râles that become coarser when edema supervenes. Not infrequently a dry pleuritic rub can be detected.

Laboratory Diagnosis.—The plague bacillus is usually easily demon-

strated, as it occurs in large numbers in the juice of the affected lymph-nodes and in the bloody sputum of pneumonia patients. For staining, Gram's method is best. The crucial test is the pathogenicity of *Bacillus pestis* toward rats and guinea-pigs, and especially its ability to infect through the shaved, intact skin. The morphologically similar bacteria do not cause disease in man.

Differential Diagnosis.—Bubonic plague may be confused with *glandular fever*, in which the nodes are, however, harder and more discrete. Prostration is less marked than in plague. *Bacillus pestis* is absent from the enlarged lymph-nodes.

Prognosis.—From the time of the medieval European epidemics the prognosis of plague has been recognized to be very uncertain. Patients thought to be out of danger may suddenly die, while those supposedly moribund at times recover. Subjects who become rapidly apathetic, with rapid weak pulse, and corresponding signs of cardiac failure, are likely to die. In India in a series of 15,840 hospital cases the mortality was 73.48 per cent. In Bombay Presidency among 392,385 cases the mortality was 79.53 per cent. For pneumonic patients the prognosis is absolutely bad.

Prophylaxis.—Personal Prophylaxis.—In 1897 Haffkine introduced the use of a bacterial vaccine which is essentially composed of intact bacilli and autolytic products of a four to six weeks' culture of *Bacillus pestis* in meat infusion broth. The dose is 3 c.c. subcutaneously for a man and proportional for women and children according to weight. Following the injection there is a marked local and general reaction, tenderness and swelling at the site of inoculation, a rise of temperature to 102° or 103° F., and malaise which lasts for a day or two. The local symptoms may persist for a week or more. Frequently the dose is administered in two or three injections at intervals of seven to ten days. Sensitized vaccine, as well as that which has been stored for four to six months, causes less local reaction and, according to some investigators, gives a higher degree of immunization. Strong's vaccination with attenuated living plague bacilli has not come into general use, although it produces higher immunity than do killed cultures. Other modifications, *e. g.*, those of Iustig and Galeotti and of the German Plague Commission, have their advocates, but are not widely accepted. From a study of a group of reliable observations on the results of Haffkine's vaccine, de Iangen and Hoesen conclude that the morbidity among those inoculated was three times and the mortality ten times less than among non-inoculated individuals.

When near patients with pneumonic plague a mask must be worn. A simple and efficient form is made by folding a piece of gauze 30 by 100 cm. (1 x 3 ft.) so as to enclose a layer of unsterilized raw cotton 10 x 20 cm. in size, and 2.5 cm. (1 inch) thick. The ends are cut into ribbons, by which the mask is tied around the head to cover the mouth and nose. Bits of cotton should be stuffed into the angle between the cheek and nose if necessary. Goggles are desirable to protect the eyes, but may prove impracticable in extremely cold weather.

General Preventive Measures.—*Bubonic Plague.*—The principles of general prophylaxis are based on the fact that plague is transmitted from rats to man by rat fleas. Bubonic plague is not spread from the human patient. Diminution or extermination of the rat population and protection against infected fleas are, therefore, essential and may be accom-

plished by starving, poisoning, trapping, and gassing rats, and by building, reconstructing, or rat-proofing buildings so that rats cannot breed. If a building is made and kept free from rats, their fleas cannot reach man. In rat destruction, snap traps have proved about ten times as effective as cage traps and more than sixty times as effective as poisoned bait. In stopping the spread of plague the most important measures are the prevention of transportation of rats or their fleas from the infected area by ships, trains, and other means of transport.

Pneumonic Plague.—Patients with bubonic plague must be watched constantly for the early signs of pulmonary involvement, for as soon as these appear strict isolation is necessary. All attendants must be masked. During epidemics the infected area must be isolated and supplies of food, fuel, and other necessities transported under suitable regulations. In urban districts daily inspection and removal of patients to plague hospitals, suspect hospitals, and contact barracks should be undertaken. Inasmuch as all patients die, the direction and rate of spread can be traced. Railways scatter the disease very rapidly. Strict isolation of subjects and contacts stops an epidemic speedily and surely.

Treatment is unsatisfactory. Symptomatic therapy is indicated to render the patient comfortable. There is evidence that antiplague serum in large doses (50–100 c.c. intravenously two or three times a day) is of value for bubonic plague, although not all careful observers have confirmed this fact. Small doses subcutaneously or large doses given late are futile. There is no rational treatment for pneumonic plague.

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ASIATIC CHOLERA

(*Cholera Indica*)

Definition.—Cholera is an acute specific infection involving primarily the lower portion of the ileum. It is characterized by profuse, effortless diarrhea, vomiting, collapse, muscular cramps, and suppression of urine.

History.—The disease is undoubtedly of great antiquity, having existed in India from time immemorial. Invasion of other countries, however, did not occur until modern times, the first wide-spread epidemic in the Orient occurring in 1817. With the increase of travel and with little knowledge of epidemiology great pandemics arose in which cholera traveled to Europe by either of two main paths: (1) Overland to Russia by the caravan routes, or

(2) by water along the trade routes of Arabia and Egypt. From Europe the disease has invaded North America, and has several times appeared on the eastern seaboard and along the Mississippi Valley. Cholera has not yet been carried from the Asiatic coast across the Pacific Ocean to our western seacoast.

Etiology.—During the pandemic between 1879 and 1883 Koch, working in Egypt, described the *Vibrio choleræ*. In view of the insusceptibility of lower animals to cholera, he was unable to complete his postulates for determining the etiological relationship of an organism to a given disease, and some uncertainty arose concerning the causative rôle of this vibrio in cholera. Doubting the pathogenicity of the cholera vibrio, Pettenkofer and Emmerich in 1892 drank a small quantity of a bouillon culture. Pettenkofer developed a mild diarrhea, and the vibrios were recovered from the watery stools. Emmerich developed a severe attack of cholera which nearly cost him his life. Aside from this experiment several accidental infections with the cholera vibrio leave no room for doubt that it is the causative agent of the disease. The presence of virulent strains of *Vibrio choleræ* in the intestinal tract, however, does not always lead to the development of symptoms.

Bacteriology.—*Vibrio choleræ* grows readily on simple media, particularly if the reaction is neutral or slightly alkaline. It is easily stained and is decolorized by Gram's method. The organism is readily killed by heat, drying, and disinfectants. In freshly isolated cultures the vibrios are extraordinarily motile.

The cholera vibrio is imitated precisely in its morphology, staining, and cultural characteristics by vibrios which are found in the intestinal tract of man and also as "free-living" forms in nature. The distinction between the pathogenic *Vibrio choleræ* and these harmless forms can be made by utilization of Pfeiffer's phenomenon or, with much greater ease and with almost equal satisfaction, by agglutination tests with a specific serum prepared from a known strain of cholera. The injection of moderate amounts of a cholera culture into the tissues of experimental animals, such as guinea-pigs or monkeys, produces death in a few days, but does not produce the clinical syndrome of cholera; the ingestion of cultures by lower animals produces no effect except under highly artificial conditions. This point is of epidemiological importance.

Epidemiology.—For its propagation in nature the *Vibrio choleræ*, as far as we know, depends entirely upon man. The organism soon dies out in nature in competition with free living forms and is not harbored by any of the lower animals. The interepidemic periods are probably bridged over in part by human "carriers"; but the proportion of carriers after an epidemic is not large and the carrier stage is of relatively short duration. This explanation of the interepidemic periods is not altogether satisfactory, and it is possible that some as yet unknown factors come into play.

Morbid Anatomy.—An early and extreme grade of *rigor mortis* occurs in cholera. A dusky cyanotic color of the skin, the finger-nails, and the mucous membrane is noticeable. On incising the abdominal wall one is struck by the dryness and deep color of the tissues. Instead of a little free fluid in the peritoneal cavity and the other serous sacs, only a sticky residue remains. The urinary bladder is empty. The ileum, particularly the lower portion, may be reddened. As a rule, the ileum contains an abundant amount of rice-water material, though its contents may vary from a little bile-stained mucus to dark purple blood-tinged fluid. Hemorrhages may occur in the

intestine. The lymphatic tissue is prominent. Histologically, there is a subepithelial edema of the small intestine. *Antemortem* desquamation of the epithelium is rare. The renal changes have not been thoroughly studied. The kidneys often show parenchymatous swelling with an irregular cortex and distorted striations. The "wet brain" of uremia is sometimes encountered.

Invasion of the gall-bladder is common, infection taking place very possibly by direct extension from the duodenum rather than by metastatic routes. The cholera carriers presumably harbor the vibrios in the gall-bladder.

Symptoms.—The *incubation period* is short, but variable, ranging from a few hours to five or six days. The symptoms can be divided rather sharply into two groups—those of collapse and those of reaction. The disease may be ushered in with a preliminary warning of one or two days of diarrhea, or the onset be sudden with violent purging. As the fecal matter is quickly cleared from the bowel, the stools consist of almost clear water with shreds of mucus and cellular débris. Occasionally, though rather rarely, this material is very finely divided so that it does not settle out, and thus forms the characteristic rice-water stool. Shortly after the onset of the diarrhea, persistent vomiting usually develops.

Symptoms of Collapse.—A characteristic train of symptoms sets in which is closely associated with the loss of fluid from the tissues. The skin loses its elasticity, muscular cramps become severe, the eyes sunken, the voice feeble, the thirst intense, the secretion of urine ceases, and the respiration becomes rapid. The pulse is rapid and weak, the blood-pressure falls, and the heart sounds are feeble. The skin and mucous membranes are blue and the temperature of the skin is subnormal. The rectal temperature may be either normal or slightly elevated.

The loss in the elasticity of the skin is first noticed over the extremities. The skin of the hands may wrinkle spontaneously (the washerwoman's hand); or when a fold of skin over the back of the hand is lifted it does not spring back into position, but sinks down very slowly by its own weight.

Muscular cramps naturally appear first in the extremities, as the loss of fluid is felt there first of all. Native patients commonly tie bamboo thongs around the fingers and toes with the idea of preventing the cramps from spreading upward. As the cramps increase in severity, additional thongs are bound around the more proximal joints. Indeed, when such patients are admitted to the hospital it is at once suspected that the symptoms have been unusually severe and that the need of fluid is urgent. The patient either loses his voice completely or is able to speak only in a hoarse whisper. The secretion of urine diminishes rapidly and then ceases altogether on account of the great loss of fluid from the bowel and because the blood-pressure in the renal artery sinks below the point (40 mm. of Hg) which is necessary for the secretion of urine. The blood-pressure falls so low that on incising a superficial vein, such as the external saphenous, a few drops of dark thick blood exude, but no free hemorrhage occurs. The red cell count is increased by 1,000,000 or 2,000,000 per cubic millimeter on account of the loss of fluid from the body. The white cell count rises to 25,000 and even to 50,000 or 60,000 per cubic millimeter. The exact nature of the polymorphonuclear leukocytosis is unknown. The poor circulation and the consequent poor aëration of the blood stimulates the respiratory center so

that the respirations become shallow and rapid. The pulse rate increases, the temperature remains low—a condition which is exactly the opposite of that of typhoid fever, for example, with its high temperature and relatively slow pulse.

These symptoms may terminate fatally during the first few days or even hours of the disease.

Symptoms of Reaction.—Distinctly more than half of the patients ordinarily survive the period of collapse or, as it is often called, the *algid stage*. The signs of reaction are largely the reverse of those of collapse. The diarrhea subsides and even constipation may develop. The muscular pains cease, the skin becomes warm and elastic, the voice returns, and the body temperature rises. The cyanosis gives way to a bright color of the skin and mucous membrane. The respirations become deep and nearly normal in rate. The pulse, instead of being feeble and rapid, returns to about normal in rate and may become full and bounding. The blood-pressure rises to 150 or 180 mm. of Hg at systole.

Interest at this stage centers largely on whether the secretion of urine commences. In some patients the amount secreted returns more or less gradually to normal and a satisfactory convalescence ensues. In a relatively small proportion the evidences of toxemia persist, and the patient passes into a typhoid-like condition which may prove fatal.

Acidosis and Uremia.—During the stage of reaction the secretion of urine is resumed in the majority of cases, but the daily output is small (100 to 300 c.c.), the specific gravity is high, and albumin and casts are abundant. The total output may increase slowly or may diminish and then cease altogether. Uremia, not unlike that of ordinary nephritis, proves fatal in about 15 per cent. of all patients who contract cholera. It was first shown in Asiatic cholera that uremia is closely associated with acidosis. The carbon dioxid content of the blood diminishes markedly and the tolerance to sodium bicarbonate is greatly increased. In the midst of an epidemic the clinical course of cholera is fairly uniform. The severity of the disease and the mortality rise to a peak during an epidemic and then decline. As already noted, a small percentage of individuals, though infected with virulent vibrios, develop no symptoms. Occasionally a prodromal diarrhea develops without consequent severe symptoms. Rarely the disease proves fatal without diarrhea. In this condition, known as *cholera sicca*, the bowel at autopsy is frequently filled with rice-water material. In young children diarrhea is much less severe than in adults, and meningismus is of definite and frequent occurrence, though the meninges, of course, remain free from any infection.

Cause of Symptoms.—It has been suggested that desiccation may account for all of the symptoms of cholera, including the signs of toxemia. In this connection it is interesting to note that travelers lost in the desert may develop symptoms suggestive of the collapse of cholera. Under these circumstances the restoration of fluid usually produces prompt and permanent relief in contrast to the more or less transient benefit that is frequently derived in cholera from similar treatment. Furthermore, the fatal cases of *cholera sicca* suggest the existence of a toxemia other than that which results from loss of fluid. There is no evidence that the cholera vibrios produce a potent soluble toxin *in vitro* and the assumption of an endotoxin acting *in vivo* rests chiefly on hypothetical grounds.

Complications and Sequelæ.—Asiatic cholera ordinarily leaves no serious

after-effects, although in American and European patients the return to full health and vigor may be protracted over several months. Just as in acute nephritis from other causes, the renal lesions do not become chronic; indeed, normal renal function is often restored quickly. Like many infectious diseases, cholera usually causes abortion. It is assumed that the muscular cramps which appear first in the extremities develop in the uterine musculature also. The intestinal lesions heal readily and no after-period of diarrhea or constipation is to be anticipated. In the great majority of cases the vibrios disappear promptly from the stools. A small but important number of patients remain carriers for weeks and even months, but not for years, as in typhoid fever.

Diagnosis.—During an epidemic any patient who suddenly develops coma or collapse should be sent to the cholera hospital for observation. Acute diarrhea following poisoning by alcohol, ptomains, or the heavy metals may simulate cholera closely. In these conditions vomiting usually precedes the diarrhea, whereas the reverse is true in cholera. An accurate diagnosis can be made only by bacteriological methods. Since agglutinins develop in the blood rather late in the disease, reliance is placed on the isolation of cholera vibrios from the stools and their identification by agglutination with a specific serum. The vibrios occur in such great numbers in the stools and grow so rapidly that routine diagnoses are easily obtained in twenty-four hours. The usual method for the examination of stools consists in the inoculation of peptone water with a little rice-water material. The vibrios, if present, grow abundantly near the surface of the liquid. After eight hours it is sometimes possible to make an agglutination test directly on this fluid culture, though it may be necessary to subinoculate this enriched material on an agar plate and examine individual colonies.

For the examination of carriers a selective medium is very helpful. The standard medium for this purpose is a very strongly alkaline blood-agar (Dieudonné's). This allows free growth of various vibrios and of some of the streptococci, but restrains effectively the great mass of fecal bacteria. In the examination of carriers it is important not to use purgatives, for after taking magnesium sulphate carriers have been known to develop a typical fatal attack of cholera.

Prognosis.—The mortality in cholera varies distinctly not only in different epidemics, but during the course of a given epidemic, being greatest at the height of an outbreak. Under ordinary conditions, with patients coming under treatment rather late in the stage of collapse, a mortality of 50 per cent. may be expected. Of this number, about 30 to 35 per cent. die in the stage of collapse, and it may be expected that 15 per cent. will die of uremia unless alkalies are used intensively. Under more favorable circumstances when the patients report early for treatment the mortality may be restricted to 25 or 30 per cent. In exceptionally severe epidemics it may occasionally rise to 75 per cent.

Prophylaxis.—Cholera is spread in much the same general manner as typhoid fever. The vibrios leave the body by way of the feces and the vomitus, but rarely by the urine. Epidemics and pandemics of cholera have arisen with a severity unknown in typhoid fever; nevertheless in certain tropical climates cholera is more amenable to prophylactic measures than typhoid fever.

Control of an epidemic of cholera can be brought about by: (1) Protec-

tion of the supplies of food and water from contamination; (2) destruction of the excreta of patients; (3) prophylactic inoculation for reducing the susceptibility of the population. The individual can protect himself with comparative ease in times of an epidemic. The recommendation to use only *hot food* and *drink* is particularly good. The vibrios are easily killed by heat, and food and water, though properly heated, can, after cooling, become seriously contaminated in a very few hours. In several tropical communities the public has been instructed thoroughly in preventive measures, and the educated adult who contracts cholera frequently receives little sympathy from the community in general.

For *specific immunization* against cholera, suspensions of vibrios killed by heat may be injected subcutaneously without any more inconvenience to the individual than if sterile saline had been used. It is probable that a moderate degree of protection exists for a few months after inoculation. This in itself would be of great assistance in controlling an epidemic. The theoretical basis for this form of inoculation is less satisfactory than in typhoid fever. The vibrios are limited almost entirely to the intestine, whereas *Bacillus typhosus* regularly sets up a bacteriemia.

Treatment.—There are three objects to be accomplished in treatment, namely, (1) the relief of toxemia; (2) the restoration of fluid; (3) the prevention of acidosis and uremia.

Many *specific antitoxic sera* have been prepared for cholera, but they have not proved of value. Indeed, no soluble toxin of the cholera vibrio has yet been isolated; until at least the general nature of the toxemia in cholera is known it is hardly feasible to prepare an antitoxin. Suspensions of *kaolin* have been used to absorb the toxic substances present in the intestinal tract. Some of the early reports regarding this method of treatment were very encouraging, but the results, on the whole, have been unfavorable.

The *restoration of fluid* is undertaken by intravenous injection of salt solution. Usually 2 liters of fluid are given in the course of fifteen or twenty minutes. The immediate effect is striking: the blood-pressure rises, the pulse and respiration become slower; the skin becomes less cyanotic and resumes its elasticity; the patient, instead of tossing about restlessly, lies quietly and comfortably in bed; the voice returns. The first request is usually for a glass of water. This does not mean that the injection of saline has made the patient thirsty, but rather that with increasing comfort he is able to make his wants known. Very few of these patients, however, proceed to an uninterrupted recovery. On the contrary, the profuse diarrhea continues, and unless the supply of fluid is maintained the symptoms of collapse return, often with increasing severity. An average patient requires the intravenous injection of 2 liters of fluid every six or eight hours for one or two days. Some patients, apparently moribund, may require injections of this amount of fluid every two or three hours for a day or more. One of the gratifying features of treatment is that apparently hopeless patients may unexpectedly react and make an uninterrupted recovery. The inspection of the patient, the character of the pulse, and the amount of fluid lost by the bowel furnishes an adequate guide for the frequency of injections. Various tests have been devised for this purpose, such as the determination of the specific gravity of the blood. In the opinion of the writer, fluid should be supplied freely before the specific gravity of the blood is increased beyond normal limits.

Acidosis and Uremia.—In Asiatic cholera the urine is sharply acid even after massive injections of sodium bicarbonate (90 gm. within twenty-four hours). In a normal person 5 gm. of bicarbonate ordinarily renders the urine alkaline. Accordingly, it is clear that in cholera the tolerance to bicarbonate is increased. Investigation has shown that this is due to the existence of an acidosis in the sense that the fixed bases of the blood and other tissues of the body are depleted. This acidosis is closely associated with the acute nephritis and uremia, but it is not specific for cholera infections. The conditions in cholera are favorable for the treatment of the accompanying acidosis. During the stage of collapse a slightly alkaline solution (0.5 per cent. sodium bicarbonate and 0.5 per cent. sodium chlorid) may be used intravenously. As the stage of reaction sets in the quantity of bicarbonate should be increased (to 1.5 or 2 per cent.) and the chlorid omitted. The injections of bicarbonate should be continued until the urine becomes alkaline or is very liberally secreted. The early and persistent use of alkalies has practically eliminated death from uremia in cholera.

General Measures.—The patient is naturally glad to remain in bed. During the algid stage hot-water bottles and light blankets afford the much desired warmth. The vomiting, which during the first days of the disease prevents the administration of even water by mouth, may be checked temporarily by small doses of *cocain* (1.8 grain) by mouth. *Digitalis* is very useful in regulating the action of the heart. During the period of reaction small amounts of liquid food may be given, but solids should be added very gradually.

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MALTA FEVER

(*Mediterranean Fever, Cyprus Fever, Undulant Fever, Bruce's Septicemia, Neapolitan Fever, Gibraltar Fever, Danube Fever, Septicemia Melitensis*)

Definition.—Malta fever is characterized by febrile attacks which persist for weeks or months, with many remittances. It is caused by *Micrococcus melitensis*, and is usually spread by goat's milk.

History.—Malta fever is an ancient disease. Hippocrates described a long-continued fever with short apyrexial intervals lasting one hundred and twenty days, which in all probability was Malta fever. During the eighteenth and nineteenth centuries Howard, Hennen, and Davy described a disease which appears to have been Malta fever. Much confusion was caused in Malta during the Crimean War by the presence of both Malta

fever and typhoid. Nevertheless, the disease was first recognized in Malta as a specific entity. Bruce in 1886 proved that Malta fever had a definite etiology when he discovered in the spleen a micrococcus which bears his name. A year later he cultivated the organism on agar and was able to reproduce the disease in monkeys by inoculation. In 1891 he obtained the organism from blood which had been aspirated from the spleen during life. In 1897 Wright and Semple showed that a diagnosis could be made by agglutination tests. In 1904 the British Admiralty, the War Office, and the Civil Government of Malta appointed a commission to investigate the disease. This Commission showed that the organism leaves the body for the most part in the urine and that it is capable of existing for a long period outside the body. It was also discovered that the milk of many goats would agglutinate the micrococcus, and later the germ was isolated from goat's milk. Manson cautions that unless serum tests are made with fresh blood and proved cultures, erroneous results may follow. Prophylactic measures have resulted in reduction of Malta fever among the British troops in Malta from 643 cases in 1905 to 1 case in 1910, and the virtual disappearance of the disease since that time except for the disruption created by the war, which made hygienic measures impossible of application.

Incidence and Geographical Distribution.—The endemic foci may be said to exist along the coast of the Mediterranean. Spain, Portugal, France, and the Levant have been almost continuously infected. Malta fever has been reported in the Punjab, India, and to a limited extent in Ceylon. Strong, twenty years ago, saw one case in the Philippine Islands, but confirmed subsequent cases have not been observed. Isolated cases sometimes occur in England and the United States. During recent years several small outbreaks have been reported from Texas. It is more than likely that a careful examination would reveal the presence of the disease in other countries.

Etiology and Bacteriology.—Malta fever is caused by the *Micrococcus melitensis* (Bruce). The organism is pleomorphic, about 0.3 micron in diameter, and occurs most typically as a coccus, although Hiss and Zinsser describe it as a bacillus; others call it a coccobacillus. Various observers have formulated the hypothesis that another closely allied organism is associated with the disease in addition to the *Micrococcus melitensis*, but no definite proof has been obtained. The organism is found in the spleen, liver, kidney, lymphatic, and salivary glands. It has been found in the stomach of mosquitoes which have fed upon patients, but there is no proof that either mosquitoes, flies, or fleas are concerned to any considerable extent in the transmission. The coccus is very resistant and lives for at least eighty days in dust, and for a period of a month in either fresh or salt water. It has, however, never been found naturally in dust or water; 10 per cent. of the goats of Malta harbored the organism. The goats are apparently healthy, although they occasionally suffer from chronic mastitis. The disease is conveyed to man by the milk of infected goats, and, as a rule, has disappeared when milk has been made safe. Other methods of infection, however, are suspected. It has been assumed that the disease may spread through the respiratory passages after inhalation of dust which has been contaminated with goat's urine. Abrasions, wounds, and cuts may also be portals of entrance. The method of spread from goat to goat is unknown. Exceedingly minute quantities of a culture serve to infect; the prick of a contaminated needle is often sufficient. Infection is reported to have occurred in areas not known to be infected when a clinical thermometer has been placed in the mouth of a healthy subject after being used by a patient with Malta fever. The most susceptible age is between six and thirty years. Individuals who have lived a long time in endemic areas appear to be immune, but this may be due to their having had the disease in childhood.

The greatest number of cases occur during the summer. The incidence curve begins to rise in April, reaches its maximum during July and August, then gradually declines until February.

Morbid Anatomy.—The *Micrococcus melitensis* may be said, as a rule, to enter the system through the alimentary tract and produce septicemia. It may be found in the heart, blood, and nearly all the internal organs. The marked enlargement of the spleen at times causes confusion with typhoid fever. Many attempts have been made to transmit the disease through mosquitoes and other biting insects, but so far these experiments have been inconclusive. Bruce feels that one attack does not confer immunity, and other distinguished clinicians agree with him. Agglutinins are formed about the fifth day and may be regarded as specific. The average infected spleen weighs over 500 gm., is soft, and shows an increase in the number of lymphoid cells. There is enlargement of the liver, with congestion of the kidneys and other abdominal organs. The colon may be ulcerated, especially if there has been hemorrhage. The lungs are congested and may show patches of consolidation.

Symptoms.—Monkeys fed with infected milk manifest the disease after fifteen days. In man, according to Johnstone, the *incubation period* is fourteen days. The disease has, however, been known to develop within six days. The *onset* of the disease is gradual. The predominant characteristic is fever without immediately evident cause, which does not usually stop the patient's work. The temperature rises gradually and the symptoms are much like those of typhoid. After several days there are usually severe pains in the back and limbs. Headaches become intense and loss of appetite is pronounced. The temperature at this stage is approximately 103° F. (39.5° C.). The fever is continuous in character, and after several weeks may decline so that the patient feels somewhat better. A few days later a relapse occurs and the same symptoms reappear. In brief, the symptoms are those of septicemia. The *relapses* may continue as long as the original fever, but, as a rule, are shorter. As one relapse follows another, the illness may persist for many months. The temperature then becomes undulating and the patient appears anemic and weak. Many patients persist in their activities while they have the fever; this usually aggravates the disease.

The symptoms are rarely as severe as the temperature would indicate. The *indigestion* may be accompanied by constipation or diarrhea. Often the *gums* become spongy and bleed on pressure. The *spleen* is enlarged and painful. The patient is usually miserable and complains of headaches and pains all over the body. *Insomnia* and *hysterical manifestations* are common. Acute delirium is rare. The *perspiration* usually has a disagreeable odor and, although continuously profuse from the beginning of the disease, is usually worse in the morning. Sudamina often occur after the third week. Sometimes the *joints* become swollen and painful, but the skin over them seldom is reddened. The hip-, shoulder-, ankle-, and knee-joints are those most commonly involved. The *blood* shows a secondary anemia (a loss of 20 to 40 per cent. of the corpuscles), its hemoglobin content is markedly reduced, and there is some poikilocytosis. The phagocytic and bactericidal powers are diminished. Agglutination takes place in dilutions of 1 : 50 within thirty minutes and is so characteristic as to determine diagnosis. The *urine* seldom contains albumin or granular casts. The *Micrococcus melitensis* is sometimes found in the urine two years after an attack. The

continuous fever for months renders the patient extremely anemic and prostrated.

When improvement is imminent the length of the intervals between the febrile attacks gradually increases until recovery takes place. The tongue clears and the remaining symptoms abate. Sometimes convalescence begins as early as the twentieth day, but cases have been known to last nearly a year. A fair average period is three months.

The severity of the disease varies: some outbreaks are characterized by very violent symptoms, the temperature rising at once to 104° or 105° F.; while in others there may be only intermittent symptoms. At times the clinical picture is much like that of typhoid. The blood changes are not distinctive. There is a gradual reduction in red blood-cell count—usually to 2,500,000 or less. There is an *ambulatory type*, of which the patient may not be aware, which often produces positive blood reactions over long periods of time. A *para-Malta fever* has also been described which is attributed to the *Micrococcus paramelitensis* of Negre and Raynaud. Its existence, however, lacks reliable confirmation.

Complications.—Ulcers may occur in the small and large intestine and give rise to hemorrhage. Nosebleed is common. There may be very high fever, pneumonia and pleurisy with effusions, or cardiac failure. Orchitis is very common.

Sequelæ.—Probably the commonest sequel is neurasthenia.

Diagnosis.—A prolonged fever, profuse perspiration of peculiar odor, the joint symptoms, the relapsing character of the fever, and the positive blood agglutination make it possible to recognize the disease. Malta fever is often mistaken for *typhoid fever*, but the blood examination reveals the difference. *Kala-azar* also resembles Malta fever, but the blood parasite typical of that disease should furnish a reliable means of differentiation.

Prognosis.—The prospect of recovery is usually good. In some outbreaks the mortality is as low as 2 per cent., but at times it has reached 13 per cent. A persistent temperature of 104° F. (40° C.) is a bad sign.

Prophylaxis.—In accordance with the experience at Gibraltar, the disease may be successfully avoided by abstaining from the use of unboiled goat's milk. During the Great War reliance on sterile milk protected troops against the disease. The value of prophylactic vaccine has not been established.

Treatment.—The treatment is purely symptomatic. *Vaccines* and *serums* have not been successful. *Good nursing* is essential. As much wholesome food as the patient can take without disturbance is most important to replace the fever wastage. *Headaches* may be relieved with acetanilid or other coal-tar derivatives, but sometimes the pain is sufficiently severe to require the administration of morphin. The *joint symptoms* are often relieved by hot fomentations or by belladonna and opium applications. The *bowels* should be kept open; calomel has proved to be very satisfactory for this. *Mouth-washes* of mild antiseptics should be regularly employed. *Sponging* to keep down the temperature is important and adds greatly to the patient's comfort. In brief, it may be stated that the nursing treatment should be similar to that of typhoid. The diet should be liquid during the febrile periods. Precautions should be taken to *disinfect* the stools, the urine, and other discharges. Open abrasions on the skin of attendants should be sealed.

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DENGUE

Definition.—Dengue is an acute, specific, mosquito-borne fever of unknown origin, characterized by two febrile paroxysms which occur nearly always within seven days and with which is associated marked leukopenia.

History.—Prior to the eighteenth century a disease was reported in Seville which resembled the dengue fever of today, and the condition was somewhat more definitely recognized in Java at the same time by Bylon. Its distinction from a number of other similar fevers has not yet been satisfactorily accomplished. The seven-day fever of Rogers is regarded by many to be dengue, but usually it occurs in epidemic form and can be readily differentiated.

Incidence.—Dengue is often associated with yellow fever, although it occurs extensively in areas in the eastern hemisphere where yellow fever is unknown. Only recently a severe outbreak of the disease swept through the Southern States, prostrating a large part of Florida. Outbreaks are frequent in Texas. In Australia dengue is very disabling; in fact in 1921 almost half the population of Brisbane was affected in the course of a few weeks.

Etiology.—More than twenty years ago Graham claimed that the disease was transmitted by mosquitoes. He implicated the *Culex fatigans*, but had no adequate data to justify the claim. A few years later Ashburn and Craig undertook researches in the Philippine Islands which tended to confirm this belief, but before their experiments could be brought to a satisfactory conclusion the disease stopped abruptly. In 1916 Cleland demonstrated in Australia that dengue could be transmitted successfully by *Stegomyia mosquitoes*. To Sydney, which had been free of dengue for many years, he brought *Stegomyia* from Queensland where they had bitten dengue patients. When these were allowed to bite persons in Sydney the disease developed within three to nine days. Recent experimental work seems to indicate that in some areas both the *Stegomyia* and the *Culex fatigans* may be responsible for transmission. Since yellow fever has been definitely ascribed to a specific spirochete there has been much speculation and deduction as to whether dengue may not also be a spirochetal disease. Spirochetes of various kinds have been recovered from the blood, but so far no definite proof of their etiological rôle has been obtained. Intravenous injection of blood taken from dengue patients on the second day of the fever produces attacks in

healthy subjects within two or three days. There is no evidence that the disease is spread by other means than insects.

Bacteriology and Pathogenesis.—As stated above, no organism has definitely been associated with the cause of the disease. Various observers have found spirochetes in the blood at different stages of the fever. Examination of the blood, however, does show that in all acute cases there is a characteristic marked leukopenia; and it is generally possible for experienced workers in the tropics to make the diagnosis from this blood-picture alone. Cleland and Bradley were able to transmit the disease by artificial inoculation through four generations, and concluded that the virus was present in the blood within eighteen to ninety hours after the onset of the fever. So small a quantity as 0.00005 mil. was found to be infective. Roizumi, Yamaguchi, and Tonomura were able to transmit the disease through the *Stegomyia*, but not through the *Culex*. The *virus* is in the blood and can pass a filter, and the filtrate is infective. As there are practically no deaths from the disease, there has been no opportunity to study the morbid anatomy.

Symptoms.—Experimental evidence indicates that the *incubation period* may be between three and nine days, although many authors believe it to be between two and five days, or even as long as fifteen days. The *onset* is generally sudden, with severe pain (usually muscular in character), in some part of the body, often in the back. There is a feeling of extreme fatigue, and chills may occur, but are rare. A characteristic onset begins with severe pain behind the eyeballs and intense headache. There is usually very severe pain in the back, particularly in the sacro-iliac joint. In children the attack often begins with convulsions or delirium. The *temperature* rises rapidly, usually to about 103° F., but not infrequently to 106° F. The *pulse rate* is from 90 to 140 per minute. The joints are often painful, but, as a rule, passive movement does not cause pain. Change of position usually causes agony and excruciating pain in the back. There is no glandular enlargement. The constant *leukopenia* is of great diagnostic importance; the white count usually varies between 1000 and 5000. The leukocytes are normal in appearance, but there is a marked increase in the number of smaller lymphocytes. The *urine* is highly colored and may contain traces of albumin. On the third day the rapid fall of temperature is generally accompanied by profuse sweating, the passage of much urine, severe diarrhea, and bleeding from the nose. After this the patient feels very much better and considers himself on the way to complete recovery. On the fifth day the temperature again rises rapidly, but usually not above 103° F. The intermission may, however, be lacking. With the second rise in temperature a characteristic *rash* begins on the palms and backs of the hands, and spreads rapidly to the arms, trunk, and legs. The eruption is of varied character. At times it consists of small macules which gradually extend in size and coalesce until the rash resembles that of scarlet fever. This, however, is unusual. At other times small macules develop with bright red points which have no tendency to spread; there are large areas of normal skin between them. Often the eruption is absent or so faint that it can only be detected with difficulty. The second attack is rarely as severe as the first, and the third is rather mild. Fourth attacks are so extremely rare that for practical purposes they may be disregarded.

The temperature curve may vary considerably, especially after the first

attack. In most instances *convalescence* is quick and permanent, but many individuals feel below par for weeks and are easily exhausted by slight effort.

Complications.—There may be hemorrhages from the nose, stomach, intestines, or uterus. Purpuric complications have been observed, but there is good authority for the belief that these are due to a previously existing malaria.

Diagnosis.—The sudden onset with severe pain in the muscles and joints, the high temperature, and the absence of the causative organisms of similar acute diseases furnish excellent indication of dengue. The disease never develops in the absence of mosquitoes and, consequently, is never present after frost. It does not occur in the northerly countries of Europe or America. Dengue may be mistaken for yellow fever, malaria, influenza, scarlet fever, measles, rheumatic fever, smallpox, and tonsillitis. *Yellow fever* is readily differentiated by the characteristically slower pulse, the jaundice, and the black vomit. In *malaria* blood parasites are found. *Influenza* usually occurs during the colder periods of the year and produces entirely different temperature and blood-pressure changes. In *scarlet fever* there are the characteristic sore throat and enlarged glands of the neck. In *measles* the predominating catarrhal symptoms are followed by the appearance of the characteristic rash. In *rheumatic fever* there is swelling of the joints, with increased pain on passive motion. *Smallpox* is sometimes difficult to differentiate until the eruption actually appears. Enlarged and diseased tonsils serve to differentiate *tonsillitis*. In the tropics *enteric fever* is sometimes mistaken for dengue, but the continued fever, constant headache, the absence of characteristic joint and muscle pains, and Widal's reaction make correct differentiation possible.

Prognosis.—The mortality is practically *nil*. In 6000 cases recently studied in Formosa there was only one death.

Prophylaxis.—Those who are able to protect themselves thoroughly against the bites of *Stegomyia mosquitoes* are usually able to escape the disease. For this purpose it is necessary to sleep in properly screened rooms or under well fitting mosquito bars.

Treatment.—There is no specific therapy and the treatment of the disease should be that for any simple fever. It is usually well to administer 0.1 grain of calomel every half-hour until the bowels move freely. Great relief can be obtained from the use of salicylates—aspirin or sodium salicylate. Occasionally hypodermic injection of morphin ($\frac{1}{6}$ grain) may be necessary to relieve pain. During the febrile periods the patient can be made comfortable by sponging with ice-water. Cold drinks should be given freely. The usual fever diet is indicated. It is important to insist upon rest in bed and to guard against too strenuous activity during convalescence in order to protect the heart against strain.

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HYDROPHOBIA

(*Rabies, Lyssa*)

Definition.—Hydrophobia is an acute infectious disease of certain animals, caused by a virus which may be communicated by inoculation to man. Infection usually results from the bite of a rabid animal, the virus being carried in the sputum.

History.—Records of the disease have existed from the time of Aristotle (about 300 B. C.). The saliva of rabid animals, however, was not shown to carry the virus until 1804. In 1884 Pasteur established the entity of the disease. He demonstrated that the nerve tissue of the cerebrospinal canal contained the virus in a pure condition, and that animals could be immunized against rabies by inoculations with an attenuated virus.

Incidence.—The disease occurs in all parts of the world except where the quarantine law with regard to dogs is rigidly enforced, as in England and Australia.

Not all persons bitten by a rabid animal develop the disease, the site and number of bites influencing its development. About 40 per cent. of dogs, and 16 per cent. of human beings who are exposed, become infected.

Etiology.—Most animals are susceptible to the disease, but it is propagated chiefly by the dog. The exact nature of the causative agent has not been determined. The virus is contained chiefly in the nervous system and salivary glands and is conveyed by the saliva. The evidence that the Negri bodies are the cause of the disease is strong, but not as yet absolutely conclusive. There is evidence of division in the bodies, both by segmentation and by budding—phenomena which account for the rapid spread of the organism, and for forms small enough to pass certain filters. Whatever their nature, the morphological specificity of the Negri bodies has been accepted.

The virus of rabies is readily filtrable, and is more or less resistant to certain agents, such as glycerin and carbolic acid, as well as to extreme cold. It gradually deteriorates on slow drying at a constant temperature of about 20° C. This fact was made use of by Pasteur in preparing a preventive vaccine.

Morbid Anatomy.—The disease is characterized by an accumulation of lymphocytes around the blood-vessels and nerve-cells, particularly the motor ganglion cells of the central nervous system. Especially helpful in diagnosis is the accumulation of lymphoid and endotheloid cells around the nerve-cells of the sympathetic and cerebrospinal ganglia. Negri has described irregular bodies, probably protozoa, which are widely distributed throughout the central nervous system. These are accepted as a dependable means of establishing diagnosis. They vary from 2 to 14 micra in length, are plastin-staining, and each body contains a variable number of minute chromatin-staining granules.

At autopsy the only gross change is congestion of the central nervous system and of the salivary and other glands. The condition of the stomach in dogs may be of aid in diagnosis. It is usually empty of food, but may contain a mixture of foreign substances, such as pieces of cloth, hair, leather, wood, and straw.

Incubation.—The location of the bite appears to affect the incubation period more than the number and depth of bites. The nearer the bite to the brain the shorter the period.

The average limits of incubation in man are three to eight weeks. The absolute limits given are eight days to several years. However, the data in the cases reported as occurring one year or more after the bite are not absolutely reliable.

In dogs the limits are from eight days to one year, with an average of two to eight weeks. In cats and swine the period is slightly shorter, and in cattle and horses somewhat longer.

Symptoms.—The clinical manifestations of hydrophobia fall into three stages:

1. *Premonitory Stage.*—The patient becomes conscious of irritation, pain, or numbness around the bite, and is melancholy and depressed. The voice is husky and he has difficulty in deglutition. The temperature may be slightly elevated and the pulse increased. The patient suffers from headache, loss of appetite, insomnia, increased sensibility, and irritability.

2. *Stage of Excitement.*—Great excitability and restlessness with extreme hyperesthesia develops. The slightest stimuli cause violent reflex spasms, particularly of the larynx and mouth. These spasms are painful and are accompanied by extreme dyspnea. Attempts to drink water cause intensely painful spasms, so that the patient dreads the very sight of water. Hence the name of the malady. Maniacal symptoms at times accompany the spasms, but the mania is rarely dangerous in form. The temperature usually varies from 100° to 103° F., but occasionally is afebrile. This stage lasts from one and a half to three days. In the intervals between spasms the patient is quiet.

3. *Paralytic Stage.*—The paralytic stage follows that of excitement, and lasts for six to eighteen hours. The patient then becomes quiet, and gradually unconscious. The heart's action is weak, and death from syncope results.

Another type of rabies is occasionally observed, but is less common in man than in animals. The first symptom is a feeling of heaviness and numbness in the extremities. Then ataxia and progressive paralysis rapidly develop. Death occurs in from two to eight days from paralysis of the heart. This type is spoken of as "paralytic" (dumb) rabies.

Diagnosis.—In man, the diagnosis is usually simple. Acute bulbar paralysis may occasionally resemble hydrophobia, and one form of tetanus has symptoms which simulate those of hydrophobia. Tetanus, however, usually begins with trismus; the spasms are tonic rather than clonic in character and do not involve especially the muscles of deglutition and respiration. The peculiar mental symptoms of hydrophobia are also lacking. Any toxin or poisonous drug which primarily affects the brain may produce symptoms which necessitate differential diagnosis.

The condition known as *pseudohydrophobia* or *lyssophobia* is a hysterical manifestation which may develop in neurotic persons following the bite of a dog. Symptoms develop earlier than those of rabies and there is often obvious imitation of a dog, especially with respect to barking and biting. Furthermore, in *lyssophobia* a true respiratory spasm does not occur.

The Biting Animal.—If the patient has been bitten by an animal that cannot be proved rabid clinically, laboratory tests are of great aid. These are (1) the microscopical test, (2) animal inoculation.

(1) The microscopical test consists in the demonstration of the Negri

bodies. The rapid spread method recommended by Williams (1904) is generally used. If Negri bodies are found, the case is considered one of rabies.

(2) When partly or completely air-dried, the smears are fixed for about ten seconds in neutralized methyl alcohol (c.p.) containing $\frac{1}{10}$ per cent. picric acid. The slide is then blotted with fine filter-paper and stained with the following preparation:

	Parts.
Saturated alcoholic solution of fuchsin	0.5
Saturated alcoholic solution of methylene-blue	10.0
Distilled water	30.0

The stain is poured on the smear, which is held over the flame until steam arises, and is then washed in tap-water and blotted. The Negri bodies are stained a magenta color, the nerve-cells blue, and the red blood-cells yellow or salmon color. If no Negri bodies are found, an intracerebral inoculation is made into each of 3 guinea-pigs. If the animal was rabid, these pigs usually show symptoms in nine to twelve days.

Prognosis.—When the disease is once well established, it is hopelessly incurable, and palliative treatment with powerful sedatives, such as chloroform and morphin, is all that can be offered.

Treatment.—Prophylaxis by the muzzling of all dogs is very essential, and its rigid enforcement has led to practical eradication of the disease in certain countries. Preventive inoculation of dogs is recommended.

In the case of a bite from an animal suspected of having rabies, *bleeding* should be encouraged and the wound freely opened. After washing with bichlorid of mercury solution (1 : 1000) thorough cauterization of every part of the wound with pure concentrated nitric acid should be done as soon as possible. If this can be done within twenty-four hours, it practically always prevents development of the disease.

Preventive Inoculation.—The so-called Pasteur treatment for rabies was introduced over forty years ago by Louis Pasteur. It is now firmly established as a prophylactic measure and should be given to every patient who is bitten by a rabid dog. The vaccine is made from spinal cords of rabbits that have been inoculated intercerebrally with rabies virus of fixed virulence. The rabbits are killed on the seventh day after the inoculation, and the spinal cords removed aseptically. Several methods have been recommended for the further steps in the preparation of rabies vaccine. The following is a modification of the original Pasteur method:

The cords are dried in sterile aspirator bottles over caustic potash at 20° C. (70° F.) for one to eight days, thus a graduated series of weaker doses is obtained. After twenty-four hours' drying the cord is known as one-day cord, after two days, as two-day cord, etc. The patients are inoculated subcutaneously every day for twenty-one days with definite quantities of emulsions of these cords. Each dose contains $\frac{1}{2}$ cm. of the cords of different strengths. The virus is preserved with carbolic acid, 0.25 per cent., and the vaccine may be sent by mail. If this vaccine is given soon after the bite of a rabid animal the mortality is reduced from 16 per cent. to less than 0.5 per cent.

When symptoms of rabies have already developed symptomatic treatment may be employed, such as will control the convulsive paroxysms,

injections of morphin, or inhalations of chloroform. Osler recommends the local application of cocain to diminish the sensitiveness of the patient's throat.

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MEASLES

(*Morbilli, Rubeola*)

Definition.—Measles is a communicable disease which prevails, most frequently, in epidemic form during the winter and spring months. The disease has an incubation period of about fourteen days and a period of invasion of three or four days. Catarrhal inflammation, fever, and an enanthema are the outstanding symptoms in this stage. This is followed by a maculopapular eruption extending over the entire body, and an exacerbation of the local and constitutional symptoms. The height of the eruptive stage is soon reached and, unless complications develop, the fever rapidly subsides and the eruption fades, leaving a fine, bran-like desquamation of the skin. Few die of the disease itself. The high mortality which makes measles one of the most feared of infectious diseases is due to the complications.

History.—Although references to measles are contained in the writings of the Arabian physicians (Razes), it was not clearly differentiated from other exanthemata until the seventeenth century. To Sydenham belongs the credit of recognizing measles and scarlet fever as separate diseases. Panum and his collaborators, in the epidemics in the Faroe Islands (1846), made noteworthy observations regarding this disease. They called attention to the time which elapses between the date of infection and the appearance of the eruption, to the disease being spread by direct contact, and to quarantine as being the most reliable means of preventing its spread. Priority of the recognition of Koplik spots is claimed by Reubold (1853), Filatow (1895), and Flindt (1896). The diagnostic significance of this discovery, however, is due to Koplik (1896). Important information concerning the nature of measles has accumulated slowly. While Hume (1758) and Mayr (1852) are said to have transmitted measles by inoculating the catarrhal secretions into children without the disease, it remained for Hektoen (1905) to reproduce the disease in individuals with blood taken from patients with measles. The first investigators to produce the disease in monkeys were Goldberger and Anderson (1910). The use of convalescent serum as a means of affording temporary immunity to measles, as advised by Chapin (1918), has met with much success.

Incidence.—Measles prevails in all climates and affects all races and nationalities. It is endemic in large cities and recurs in epidemic form with almost periodic outbursts at intervals of one, two, or three years. The epidemics appear with such regularity that they may be predicted with a fair degree of accuracy. Statistics show that they occur during the winter and spring months more frequently than in the summer and fall of the year. Among 530 epidemics occurring in Europe and North America, 63.7 per cent. were observed during the colder and 36.3 per cent. during the warmer months of the year. Seasonal variations affect the mortality rate but little.

Measles is regarded as a disease of childhood, as 97 per cent. of the cases occur before the fifteenth year and over one-half of the cases are reported during the first five years of life. It is a disease of the child because of the extremely high susceptibility of individuals to it, its wide prevalence and ease of communicability, the lack of a recognized means of prevention, and the immunity that one attack confers. However, it may occur at any age. When introduced into a community where the disease has not prevailed for many years individuals of all ages are attacked. Thus, in an epidemic in Iceland, 47 infants in the first months of life were attacked, while in other epidemics patients of eighty years or more have been affected. Measles occurring in the pregnant mother is apt to be followed by miscarriage. While ordinarily the infant *in utero* is not infected, instances are reported in which the infant is born with the eruption or develops the disease shortly after birth.

Prior to the fourth month infants enjoy a remarkable immunity. Pirquet states that before the second month measles is unknown in infants whose mothers have had the disease. This immunity rapidly disappears and it is doubtful whether a natural immunity ever exists. The so-called "natural immunity" which individuals show might be spoken of more properly as (1) pseudo-immunity from isolation, and (2) acquired immunity. In the first class are those individuals who have come through childhood and adolescence and finally contract measles in adult life. During the mobilization of troops in the winters of 1914 to 1918 great epidemics occurred in the training camps. The soldiers from the rural districts contracted the disease, while those from the cities escaped. The immunity existing in this class before their infection was merely a pseudo-immunity resulting from the protection afforded by natural isolation of rural segregation. In the second class certain very small groups of individuals are found who, though repeatedly exposed during infancy, give no history of ever having had the disease, and they never contract it. Apparently such individuals do acquire an immunity during infancy, from repeated exposures, which protects them throughout life. This is probably an acquired immunity.

Measles is more rapidly transferred than any of the other communicable diseases. Only occasional instances are seen in which a child when exposed, no matter how slightly, fails to develop the disease. Whereas second and even third attacks of measles are reported, they are not met with very frequently and, as a rule, one attack affords absolute immunity.

Etiology.—A number of different micro-organisms which have been held as the cause of measles have been described by various observers (Tunnicliff and others), but as yet proof of their specificity is wanting. Goldberger and Anderson, Lucas, and, more recently, Blake and Trask have successfully inoculated animals with the blood and secretions from the mouth and nose of

patients with measles. They were able to produce fever and a morbilliform eruption in *Macacus rhesus* monkeys. The symptoms appeared in six to eight days. Blood was infective when taken before the eruptive period and for twenty-four hours after its appearance. The secretions were infective during the period of eruption. The virus obtained by these workers passed through the Berkefeld filter and was maintained by blood inoculations through several generations of animals.

The attempts to produce measles experimentally in man by the inoculation of blood and secretions from patients with measles have been attended by conflicting results. Mayr, Herrman, Munro, and others have reported the successful inoculation of man with the secretions from patients with measles. Hektoen has reported the successful inoculation of blood taken during the eruptive period. Sellards and Wentworth, with carefully controlled experiments, failed to produce measles in apparently susceptible individuals, either with the blood or skin lesions, or with secretions of patients secured during the pre-eruptive stage of the disease.

Although the specific cause of the disease has not been isolated, there is sufficient experimental and clinical evidence to show that the infective agent is contained in the secretions from the eyes, nose, and respiratory tract, and that the period of highest infectivity is in the pre-eruptive stage.

Dissemination.—Measles is conveyed from one person to another by the infectious material. It may be spread by direct contact with the secretions, or spread indirectly by droplet infection during coughing, sneezing, etc. The disease, while not readily transmitted by a third person, as the contagion is short-lived outside the body, may be carried to another person, unless strict precautions are observed. The rapid spread of the disease is due not alone to its high infectivity, but also to the fact that the patient is most infectious for several days preceding the appearance of the eruption. The infectivity rapidly subsides after the disappearance of the catarrhal symptoms, and probably ceases after the height of the eruptive stage is reached.

Morbid Anatomy.—The skin lesion is a proliferative and exudative reaction in the capillaries of the corium with an extension of the exudation of serum and endothelial leukocytes to the adjoining epidermis, hair sheaths, and sebaceous glands. Often small foci of minute vesicles and pustules form. The epithelial cells undergo necrosis, so that when the rash becomes evident, these lesions in the epidermis are in the process of drying up; later they desquamate as scales. Koplik spots correspond to the minute early lesions of the epidermis. They tend to macerate rather than dry up and may terminate in erosions or, if secondarily infected, in ulceration. There is a marked inflammation of the eyes, the nose, and the mucous membranes of the entire respiratory tract. It is so uncommon to see patients die with uncomplicated measles that the pathological findings are those of the *complications*. The *bronchopneumonia* is the type usually found associated with the *Streptococcus hemolyticus*, although other organisms are frequently associated. It is peribronchial and interstitial in distribution, with nodules of dense tissue and exudate about the terminal bronchioles. The bacteria spread by way of the lymphatics through the interlobular septa to the pleura. The lymphatics are thrombosed and the lung becomes thickened by new formation of tissue. A pleural exudate with organization develops rapidly. Frequently the lung becomes the seat of extensive necrosis and

often there is an effusion into the pleural cavities. Hyperplasia of the lymphatic glands and degenerative changes in the liver and spleen are almost always found.

Symptoms.—Period of Incubation.—The time elapsing from the date of exposure to the appearance of the symptoms is quite constant. Usually eight to twelve days pass before the appearance of the catarrhal symptoms, and eleven to fourteen days before the eruption makes its appearance. The incubation period is seldom less than a week and rarely longer than fifteen days. An exposed person may be regarded as having escaped infection if fever, catarrhal symptoms, and Koplik spots do not appear within fifteen days after exposure. It has been observed that patients may show a gradual loss in weight (Meunier's sign) and a leukocytosis

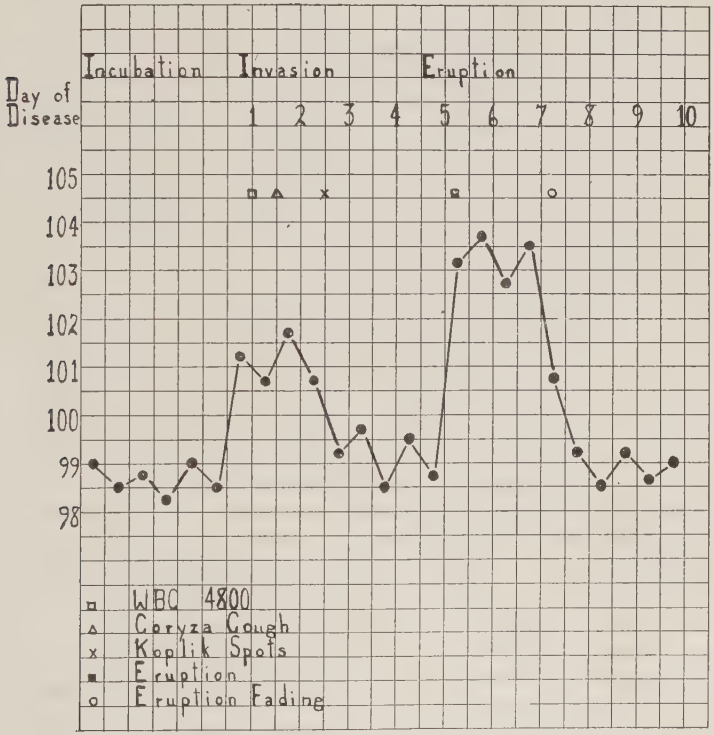

Fig. 5.—Temperature chart of a patient with measles.

toward the end of this period. Definite symptoms are seldom found before the period of invasion.

Period of Invasion.—The duration of this stage is from three to four days. The chief symptoms are a *catarrhal inflammation* of the eyes, nose, and respiratory tract, *fever*, and an *enanthema*. The symptoms may be so slight as not to interfere with the daily activities of the patient, or they may be severe from the onset. Malaise, anorexia, chilliness, vomiting, and diarrhea are usually proportionate in severity to the height of the fever and the intensity of the catarrhal symptoms. At the *onset* the mucous membrane of the eyes becomes reddened and swollen, there is lacrimation, and often photophobia. There is seropurulent discharge from the nose. The

patient becomes quite uncomfortable from the irritative discharges from the eyes and nose, the frequent attacks of sneezing, the hoarseness, and the dry hacking cough. Fever adds to the discomfort. The temperature may be 102° to 103° F., and then gradually recede by morning remissions until it is normal after two or three days. Variations in the course of the temperature are seen frequently: it may be normal in the morning, reaching 102° to 103° F. in the afternoon; or during the entire period it may range from 99° to 101° F. Its tendency to recede and return to normal after two or three days, remaining so until the rash appears, is of some diagnostic significance. Seldom does it rise rapidly and remain high throughout this stage.

The *catarrhal symptoms* and the *fever* are so often regarded as symptoms of an acute infection, that the true nature of the infection passes unrecognized until the appearance of the *eruption*. The disease should be recognized before the rash appears, as an enanthema is found in about 97 per cent. of the patients. This is known as Koplik's sign. Koplik spots are seen on the buccal surfaces as bluish-white specks, pin-point in size, surrounded by a bright red areola, most often at the level of the first molar teeth. At first only one or two may be present, but later the entire mucous surface may be covered with them. Finally, in contrast with the congested mucous membranes, the surrounding red areola becomes less marked and only fine white specks can be distinguished. They may be found as early as the second day, but usually they are not seen until a day or so before the eruption. In addition to Koplik spots the mucous membranes of the mouth are swollen, bluish-red in color, and less glistening than normal. Often herpetic stomatitis and a gingivitis are present. A blotchy, bluish-red eruption may be found on the palate before the eruption of the skin, and it is not uncommon for atypical skin eruptions to develop during this stage.

A *leukopenia* with a relative and absolute diminution of the lymphocytes is found in a large percentage of cases. This constitutes one of the characteristic findings of the disease and, as a rule, it is present before the appearance of Koplik spots.

Period of Eruption.—The eruption appears about the fourth day, after the temperature has fallen or even become normal, with or without an abatement in the intensity of the catarrhal symptoms. It is seldom seen earlier than the second day and rarely after the fifth day. The rash is noticed first behind the ears on the neck, or about the roots of the hair over the forehead. It may, however, develop elsewhere on the body. After the eruption once begins it spreads quickly over the face and neck, the upper part of the chest and back, and lastly over the lower extremities. The body may be entirely covered within thirty-six hours, although ordinarily this requires about three days.

The *lesions* first appear as dusky red macules. They rapidly increase in number and become maculopapular in form. The lesions are usually grouped together to form crescentric outlines or blotches which are separated by areas of normal skin. When the rash is fully developed they may become confluent. Even in moderate cases the eruption tends to coalesce and is most intense on the face and back. With the appearance of the eruption, the local and constitutional symptoms increase in severity. The skin itches and burns, the eyes are swollen and red, and there is a mucopurulent discharge which, with the sensitiveness to light, causes much distress.

The cough is frequent, harsh, and unproductive. The temperature rapidly rises to 103° or 105° F., and the pulse and respiration rates increase correspondingly. Variations from the usual temperature curve are indicative of the development of complications. The swollen and puffy face, the photophobia, and the purulent discharge from the eyes and nose, together with the characteristic eruption, and a dry, hoarse, racking cough, present a picture which is seldom seen in any other disease.

When the eruption has reached its height, the temperature begins to fall, so that it reaches normal in twelve to forty-eight hours. With the decline in temperature there is a rapid amelioration in both the local and constitutional symptoms. The distressing cough subsides, the catarrhal symptoms disappear, and the general condition of the patient improves rapidly.

The eruption fades in the order of its first appearance, leaving a slight brownish stain which remains for a week or more. Desquamation in the nature of fine, bran-like scales begins as soon as the rash subsides and is usually completed in five to ten days.

Whereas measles, as a rule, follows either a mild or severe course, unusual forms do occur. The fever and catarrhal symptoms may be so slight as almost to escape notice, with an eruption which is otherwise characteristic, or the fever and catarrhal symptoms may follow the usual course with an eruption which is scanty and atypical. Koplik spots are found invariably in the atypical cases. *Hemorrhagic,* or *black measles* is infrequently seen. The author has observed several patients with a true hemorrhagic form. The symptoms were characteristic of the invasion period, but with the appearance of the eruption there was marked prostration and high temperature. Petechiæ and large purpuric spots covered the entire body. There was bleeding from the mucous membranes and frequent bloody stools. *"Toxic" forms* with hyperpyrexia, cyanosis, and respiratory symptoms developing rapidly with the onset of the eruption are rare.

Complications.—The complications and sequelæ are seldom due to the toxins elaborated by the specific cause of the disease, but to the activity of such *secondary invading organisms* as the *Streptococcus hemolyticus,* either alone or associated with the *influenza bacillus,* the *staphylococcus,* or the *pneumococcus.* Likewise, the diphtheria bacillus and the tubercle bacillus resting within the body may assume activity as the result of the disease. Involvement of the eyes, the ears, the larynx, and of the larger bronchi are so frequent that they are to be regarded as symptoms rather than complications. The complications which are the most common are those involving the lungs, the ears, the larynx, and the intestines. They may occur during the invasive, eruptive, or convalescent period.

Laryngitis, appearing early in the course of the disease, may be due to a simple inflammation of the mucous membranes. Later, as the result of extensive ulcerations or a pseudomembrane, the laryngitis assumes grave significance. The symptoms may be slight—hoarseness or a croupy cough—or they may be severe, with aphonia, cyanosis, and dyspnea. The laryngitis usually subsides with the full development of the eruption, but it may persist, and occasionally relief by intubation or tracheotomy is necessary. In every case with marked laryngeal symptoms the probability of their being caused by the diphtheria bacillus must be kept in mind. *Bronchitis,* as indicated by cough and the presence of râles in the lungs, is almost always

present. These signs, even with slight fever, may persist for some time after the disappearance of the eruption. They are not of serious import unless accompanied by prostration and rapid respiration.

Bronchopneumonia, resulting from secondary infection by the invading pathogenic organisms, is of much importance and is the complication causing the high mortality. It is most frequently seen in children under three years of age and in the aged. Individuals living crowded together under poor hygienic surroundings, as in institutions and barracks, are affected more often than those in single homes. Among children of all ages it is found in about 10 per cent. of cases. Bronchopneumonia is found in practically every patient at necropsy. It may develop during any stage of the disease, but more frequently it begins during the eruptive stage. Involvement of the lungs is always to be suspected after the disappearance of the eruption when, in addition to the continuation of fever, there is prostration, rapid respiration, rapid pulse, dilatation of the *alæ nasi*, and a grunting expiration. There is usually cyanosis and a persistent unproductive cough. The fever, though not necessarily high, is most often irregular in type. Examination of the lungs may reveal râles scattered diffusely throughout both lungs. Bronchial breathing and impairment of resonance may be found only after the process has been present for some time. The disease may run its course after a week or ten days, but much more frequently it lasts three or four weeks. Empyema and chronic pneumonia are frequent sequelæ. *Lobar pneumonia* occurs rarely.

Tuberculosis.—Measles seems to favor the development of acute processes, if the patient has had a pre-existing focus of infection. Tuberculosis should always be suspected in the prolonged cases with pulmonary involvement. *General miliary tuberculosis, tuberculous meningitis, tuberculosis* of the *joints* and *bones* are common sequelæ. Measles in a tuberculous individual is of grave significance. It is of interest that a patient who has either an active or a latent tuberculous lesion will not give a positive tuberculin reaction just preceding or for four or five days after the eruptive stage.

Vomiting and *diarrhea* are frequently observed in children at the beginning of the infection. Diarrhea, especially when it continues after the eruptive period, may be a serious complication in infants under two years. All forms are seen. Enteritis with tenesmus and stools consisting of mucus, pus, and blood with shreds of mucous membrane may persist for weeks. Lesions in the ileum and colon are always found at necropsy.

Otitis.—A simple inflammation of the middle ear is seen in a high percentage of cases. *Otitis media* accompanied by pain and fever sufficient to require myringotomy occurs in about 12 per cent. of the cases. It is often resistant to treatment and persists for a long time. *Mastoid* disease and permanent *deafness* complicate measles less frequently than scarlet fever. *Gangrenous stomatitis* or *noma* due to Vincent's spirillum and fusiform bacillus are found mostly in institutional children. *Vulvitis* is also found in the debilitated patient. *Nephritis* is not common. *Endocarditis, pericarditis*, and *myocarditis*, as a result of secondary invading organisms, have been reported. *Adenitis* occurs in a relatively large number of cases, but is usually not severe and seldom goes on to suppuration. *Catarrhal conjunctivitis*, unless properly cared for, may become purulent with subsequent serious damage to the eyes, resulting from a keratitis, corneal ulceration, or panophthalmitis. *Convulsions* and *meningitis* are unusual early in

the course of the disease. When they do occur, they usually follow as sequelæ of otitis, bronchopneumonia, or tuberculosis. *Hemiplegia, transverse myelitis, optic atrophy,* and various other disturbances of the *nervous system* have been reported. In one epidemic observed by the writer four patients developed symptoms of peripheral neuritis about four or five days after the disappearance of the eruption. One patient died with a progressive involvement resembling postdiphtheritic neuritis. *Epidemics of pertussis* occurring with or following measles are seen much more frequently than epidemics of the other communicable diseases. Sporadic cases of scarlet fever, diphtheria, varicella, etc., are not uncommonly found in association with measles.

Diagnosis.—A history of exposure and the onset of catarrhal symptoms (coryza, rhinitis, laryngitis) with or without fever are suggestive of measles. The presence of a single Koplik spot completes the diagnosis. This is an early pathognomonic finding. Even with remission of the temperature and improvement of the catarrhal symptoms, isolation should be maintained until the period of invasion has passed, as Koplik spots may be late in appearing and in a small percentage of cases they do not appear. They should be looked for daily and in bright sunlight, otherwise they are often overlooked. A leukopenia with a relative and absolute decrease in the lymphocytes is of corroborative significance in the pre-eruptive stage. A leukocytosis does not exclude measles. The diagnosis should not be made from the appearance of the eruption alone. The skin eruption in other diseases, such as rubella, scarlet fever, exanthema subitum and serum sickness, as well as toxic and drug rashes may simulate it very closely. The rash in streptococcic, meningococcic, and other infections has been mistaken for measles.

Prognosis.—The mortality during the first six months of life, owing to the immunity at this age, is comparatively low. It reaches its maximum before the third year, gradually falling from then until between the sixth and fifteenth years, when it again becomes low. Children living in good hygienic surroundings have a relatively low mortality (4 to 6 per cent.), while among children living in institutions, and adults closely congregated as in a barrack, the death rate is high (15 to 35 per cent.). *Bronchopneumonia, laryngitis,* and *enteritis* are the chief complications upon which the high mortality depends. One-third or more of the patients affected with bronchopneumonia succumb to the disease. Such pre-existing diseases as tuberculosis, syphilis, and severe nutritional disturbances, and the occurrence of infectious diseases, particularly pertussis and diphtheria, lessen the chance of recovery. During the eruptive period, should the rash remain bright, a temperature of about 105° F. need not be alarming. Should the eruption appear late, or disappear suddenly with hyperpyrexia (106° to 107° F.), cyanosis, and a rapid pulse, the outlook is grave.

Prophylaxis.—Although the extreme susceptibility of individuals makes it probable that almost everyone will have measles, unnecessary exposure is unwarranted. A consideration of the high mortality renders it most important that every effort should be made to prevent its spread. Effectively protecting individuals from exposure is attended with much difficulty, as the greatest infectivity occurs at a time before the disease can be readily diagnosed. Prompt and strict isolation of the first case at the onset of catarrhal symptoms will aid in limiting the extension of the disease. The

prophylactic inoculation of children who have been exposed to measles with convalescent serum has proved a most effective means of protection. Infants and children under three years of age, those suffering from nutritional disturbances, tuberculosis, and other diseases which lower the natural resistance of the body, should, if possible, be protected from measles. It has been found that when 3 to 6 c.c. of blood-serum from convalescent patients, taken one week after the eruptive stage, is injected into the exposed patient, not later than the fourth day of the incubation period, an immunity develops in about 95 per cent. of the cases. This is a *passive immunity* which lasts about six weeks. If blood from convalescent patients is not available, then larger amounts of serum from adults who have had the disease may be used. If the serum fails to secure a complete immunity, it quite often affords a protection which limits the disease to a very mild form. Disinfection after measles is not necessary provided the clothes, mattresses, and other utensils used in the sick-room are thoroughly cleansed and aired in the sunlight. *Quarantine* regulations in measles should be continued for two weeks after the appearance of the last case.

Treatment.—There is no specific treatment. Therapy is to be directed toward relief of the symptoms, the prevention and treatment of complications. The patient should be confined to bed during the entire febrile period and until all danger of complications has passed. The room should be well ventilated, the patient protected from drafts, and separated from other patients with the disease. The eyes must be protected from intense light. Ingestion of a plentiful supply of water in the form of fruit juices with sugar is desirable in order to maintain free elimination through the kidneys, and to counteract the development of ketosis. The bowels should be kept open with laxatives. The simple diet suitable in uncomplicated cases need not be forced. The eyes should be kept clean with saline or boric acid solutions, and the lids prevented from adhering by anointing them with vaselin. Albolene instilled into the nose at frequent intervals tends to relieve the discomfort from rhinitis. When laryngitis is severe and the cough distressing, inhalations of steam with menthol or compound tincture of benzoin often afford relief. Camphorated oil applied to the chest at frequent intervals is soothing and the elimination of the camphor through the lungs ameliorates the distressing catarrhal symptoms. It may be necessary to control the cough with small doses of codein sulphate or paregoric. The ears should be examined frequently. Drops of carbolized glycerin (5 per cent. solution) and hot applications tend to relieve earache. Persistence of the temperature and of pain may necessitate myringotomy. The discomfort from the eruption can be allayed with alcohol rubs, carbolized vaselin, or alkaline baths. Antipyretics are not indicated. If the temperature is alarmingly high, alcohol sponges or tepid baths may be used to lower it and quiet the patient. Acetylsalicylic acid may be useful in relieving the general discomfort. Daily baths to facilitate desquamation should be given as soon as the rash has disappeared.

Complications should be watched for closely, and appropriate therapeutic measures instituted as they arise. With the development of bronchopneumonia, strict isolation must be enforced in order to lessen the danger from cross-infection to other patients. Essentially the same treatment is employed in measles as when bronchopneumonia arises under other circumstances. Every effort should be made to sustain the nutrition of the

patient by a suitable and adequate diet. As the process may continue over a long period of time, forced feeding should be resorted to earlier in measles than in primary bronchopneumonia. Diarrhea responds usually to limitation of food, to boiled skimmed milk, or other therapeutic foods. When it becomes severe, or if the stools contain mucus, blood, and pus, the more energetic measures as used in the treatment of bacillary dysentery have to be tried. Diphtheria antitoxin should be administered *early* to every patient with laryngitis when diphtheria cannot be excluded definitely. Carefully supervised attention during the convalescent period is of the utmost importance and, if always carried out, would prevent many of the complications.

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RUBELLA

(German Measles, Rötheln)

Definition.—Rubella is an acute, highly contagious disease, similar to but quite distinct from measles and scarlet fever. It is characterized by a long incubation period, short invasive stage, benign course, and almost complete freedom from complications.

Etiology.—Although the *specific agent* has not been definitely isolated, it is probably a filtrable virus which is present in the buccal and nasal secretions. The disease is transmitted chiefly, if not entirely, by direct contact. The possibility of infection through fomites or a third person has not been determined. The infectivity is less than that of measles and of short duration. Like measles, rubella is infectious for only a day or two before the eruption appears.

Rubella is prevalent during the first half of the year. The *incidence* begins to rise during January, becomes maximal in May and June, and then falls abruptly. The characteristic local outbreaks occur among aggregations of unprotected individuals. Although children between the ages of three and twelve years are most susceptible, young adults who have not had the disease during childhood are frequently attacked. Children who have had measles develop rubella oftener than children who have not. Infants under six months of age have a certain degree of immunity. One attack almost invariably protects against others, but not against measles or scarlet fever.

Every three or four years a more or less pronounced epidemic occurs, and occasionally an outbreak of severe rubella resembling measles is reported.

Symptoms.—The period of *incubation* varies from ten to twenty-two days, and is usually seventeen or eighteen days. A short period of pharyngeal catarrh usually precedes the rash by about twenty-four hours. Rarely a longer prodromal period of ill-defined discomfort occurs before the eruption appears. The characteristic adenitis of the mastoid, occipital, and cervical glands can, in the majority of cases, be detected a day or two before the appearance of the rash.

The *rash* is papular and morbilliform in the beginning, but frequently becomes scarlatiniform in the second stage. It appears as discrete, round, or oval spots, first on the face or neck, around the mouth or behind the ears, and occasionally on the scalp. Sometimes the wrists, chest, shoulders, or even the legs are affected first. The rash, which spreads rapidly downward, may cover the entire body in the course of a day. In most cases it fades as rapidly as it develops, so that the face is almost clear by the time the lower extremities are involved. The papules, which are smaller than those of measles, are pale pink in color and tend to cluster in small groups. The rash may be scarlatiniform on the second day. This is most marked on the trunk, especially on the back. The rash rarely persists more than seventy-two hours and hardly stains the skin, contrasting in this respect with measles.

The mucous membrane of the *mouth* is not inflamed and Koplik's spots never occur. Fine vesiculation and congestion of the soft palate is often seen. The tonsils may be slightly swollen and reddened and there may be some pharyngeal catarrh. The *conjunctivæ* are pink and the eyes slightly suffused. Photophobia is rare. The *temperature* usually rises as the rash appears, but rarely exceeds 101° F. The increase seldom lasts longer than two or three days. Often there is no fever at all.

The *adenitis*, which is very distinctive, involves the mastoid, occipital, posterior cervical, and frequently the axillary and inguinal glands. These usually become enlarged to the size of small peas, and are firm, discrete, and tender. They resolve rapidly without suppuration when the rash subsides. The blood undergoes no characteristic changes.

Convalescence is rapid. A slight furfuraceous desquamation may occur.

Complications and sequelæ are rare and trivial, although otitis, arthritis, nephritis, and endocarditis have been reported, occurring chiefly in severe epidemics. Mild recurrent sore throat, slight laryngitis, slight bronchial catarrh, mild rheumatic pains, or transient albuminuria are those more commonly observed.

Diagnosis.—Rubella is confused chiefly with the mild forms of measles and scarlet fever, especially when it is severe. *Measles* can be differentiated by the shorter incubation period of fourteen days, by the marked catarrhal symptoms, the presence of Koplik's spots, a more severe constitutional reaction, and the rash which is darker and more persistent, and stains the skin. *Scarlet fever* has an even shorter incubation period (about seven days) and is characterized by initial vomiting, headache, and high fever, and the absence of rash upon the face. Rashes caused by toxins and drugs are usually polymorphic and irregularly distributed. They are not accompanied by the glandular enlargement characteristic of rubella. *Erythema scarlatiniforme* bears a greater resemblance to scarlet fever than to rubella; it avoids the face, does not cause enlargement of the mastoid or occipital

glands, and tends to recur. *Pityriasis rosea* which is perhaps an infective fever, may be distinguished by the so-called "Herald patch" which precedes the general eruption, as well as by the usual primary localization on the upper part of the trunk. In this disease the patches are scaly, often macular and ringed. The papules, which are decidedly larger and more persistent than those of rubella, desquamate characteristically from the center toward the margin. *Secondary syphilids* bear a superficial resemblance to the rash of rubella, but may be easily differentiated.

Prognosis.—Recovery is the rule. Although rubella is known to recur, second attacks are not common. Relapses occur very rarely.

Treatment.—Prophylactic.—Exposed individuals should be isolated from the tenth to the twenty-first day after exposure to the infection. A careful watch should be kept for tenderness and swelling of the mastoid and occipital glands.

Therapeutic.—The patient should be isolated and kept in bed until all symptoms have subsided. If no complications develop, quarantine may stop after seven days, although the Association of Medical Officers of Schools advises that it continue for ten days.

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MUMPS

(*Epidemic Parotitis*)

Definition.—Mumps is a general, specific, infectious and contagious disease with a characteristic localization in the parotid, less frequently in the submaxillary and sublingual glands. Metastatic complications may occur in the organs of the genito-urinary, nervous, digestive, circulatory, or endocrine systems.

Goats, dogs, and cats have been known to suffer from parotitis similar to mumps in man.

History.—Although an epidemic of mumps was described by Hippocrates, the specificity of the disease as distinct from secondary suppurating parotitis has been recognized only during the last century and a half.

Incidence.—Mumps occurs most often in children between the ages of five and fifteen years; but young adults under thirty are still susceptible. The disease is uncommon after the age of forty, and is very rare in infancy.

Nevertheless, instances of intra-uterine transmission, as well as cases in young infants and in persons over eighty years of age, have been recorded. There is no difference in the susceptibility of the sexes.

Mumps occurs in all climates, but about six times more often during the cold months than during the warm seasons. It develops whenever children or young adults are in close contact, as in schools, barracks, camps, and ships. Epidemics are more common in the army than in civil life.

Mode of Transmission.—The contagium of mumps is in the patient's saliva, and direct transmission by the droplet method is the rule. Healthy human carriers probably exist, but have not been proved by experimental investigation. Indirect transmission by the hands or lips of a third person, or by contaminated inanimate objects is possible, but these act only over a short period. The virus is not present in food or water.

Duration of Contagion.—Transmission may occur before the parotid lesion has developed, and the contagious stage lasts throughout the period of glandular swelling. Since the parotid swelling usually disappears in seven days, the danger of contagion during the second week, when convalescence is established, is not great. In mild cases quarantine for two weeks is sufficient. Transmission of mumps as late as six weeks after recovery has been noted and seems to indicate that the convalescent had remained a carrier during that period.

Immunity.—An attack of mumps produces immunity which, as a rule, endures for life. Second attacks are comparatively rare; third and fourth attacks have been observed among soldiers.

Etiology.—There is strong experimental evidence that the specific causative factor of mumps is filtrable. It is present in the saliva during the first six days of the disease, but absent on and after the ninth day. Its presence has been demonstrated (by experiments on cats) in the blood-stream of human patients with marked constitutional disturbance, and accounts for the systemic symptoms as well as the metastatic complications. Kermorgant believes that the filtrable virus is the finely granular form of a spirochete which he has cultivated from the buccopharyngeal secretions of patients in the early stage of mumps. With cultures of this spirochete he has produced parotitis in monkeys.

The cocci which have been isolated from the saliva and from fluid aspirated from the swollen parotid glands have failed to reproduce the disease when inoculated into animals, and must be regarded as mouth contaminations.

Morbid Anatomy.—The affected glands are swollen, red in color, and moist. The cut section has a granular appearance due to swelling of the acini. Microscopical examination shows congestion of the blood-vessels, edema of the connective-tissue framework, and swelling of the epithelial cells in the acini. Cellular infiltration, chiefly mononuclear in type, occurs around the blood-vessels and ducts, which may be dilated. The adjacent lymph-nodes are swollen and congested.

Morbid Physiology.—The saliva from the inflamed salivary glands shows no change in cytology nor in fermentative action. This is because the lesion does not affect all parts of the gland equally, and normal function of some parts may be preserved. The amount of secretion is unchanged in mild cases and only rarely is greatly increased. Edema and cellular infiltration around the ducts may cause occlusion and retention of saliva.

which result in increased glandular swelling and pain, with dryness of the mouth.

Symptoms.—The *incubation period* has an average duration of eighteen days, but may vary from eight to thirty days.

The first symptom in mild cases is swelling of one, less often of both, parotids. This is accompanied by pain and stiffness of the jaw and a mild rise of temperature.

In more severe cases *prodromal symptoms*, including headache, anorexia, malaise, chilliness or a distinct chill, may be present for twelve to forty-eight hours. In children convulsions sometimes usher in an attack. Epistaxis has been noted.

Local Signs.—The parotid swelling has an elastic feeling and varies in size and in extent. It lies in front of the auricle below the zygoma and extends backward under the lobe of the ear, sometimes as far as the mastoid process. If the submaxillary gland is involved as well, the edema of the surrounding tissues may be so great as to obliterate the normal curve of the neck. In rare cases the swelling extends upward to the eye, causing edema of the lids and protrusion of the eyeball, with involvement of the lacrimal gland.

The glandular swelling usually increases for two to four days and remains at its height one or two days. Resolution is complete, as a rule, within seven to ten days after the onset, but it may be delayed as long as a year. Osler has noted chronic hypertrophy of the inflamed parotid gland instead of restoration to normal.

Should the opposite parotid gland become involved, symptoms usually appear within one to four days of the onset, but this interval may be prolonged one to six weeks.

The skin over the swollen glands is tense, but not reddened. Pain, which is a constant symptom, is rarely excessive. It is increased on moving the jaw. Earache may be present. Swelling of the submaxillary or sublingual glands is readily diagnosed by observation and palpation.

In an epidemic of 5756 cases of mumps among soldiers, Radin found both parotids involved in 2747 patients and both parotids free in 37. The submaxillary glands alone were affected in 16 cases, the sublingual glands alone only once. All three pairs of salivary glands were involved in 10 patients.

Mild redness of the pharynx or of the buccal mucosa is occasionally seen at the onset. Edema of the pharyngeal wall and pressure upon the tonsils with dysphagia may result from a large parotid swelling. Laryngeal edema and death may ensue.

The orifice of Steno's duct on the affected side is swollen and red, surrounded by a pale area of edema within a zone of minute hemorrhages.

General Signs.—There is no characteristic *temperature curve*. The mild initial rise to 37.2° or 38.5° C. lasts two or three days and increases when a second gland becomes involved. Orchitis may be heralded by a fever as high as 41.0° C.

The *pulse rate* is slowed throughout an attack, 50 to 60 beats per minute being the average. The bradycardia is apparently of nervous origin, and bears no relation to the intensity of the local lesion. The blood-pressure falls on the third or fourth day and rises to normal toward convalescence.

Prostration may be marked from the onset, and is always increased when

complications arise. The spleen is often enlarged at the height of the attack. Epistaxis may be repeated. Abdominal pain and diarrhea occasionally occur.

Blood-cell Count.—While the total leukocyte count is slightly or not at all increased, a relative and absolute lymphocytosis is the rule, and the polymorphonuclear leukocytes are correspondingly diminished. Orchitis is usually accompanied by a polynuclear leukocytosis. When the glandular swellings subside the blood-count becomes normal.

Blood-culture.—Culture of the blood by ordinary bacteriological methods gives negative results.

Course and Duration.—In most children the disease is benign, with mild general symptoms. In older subjects complications often prolong the attack. Mild cases last four to seven days; severe cases, two or three weeks.

Complications.—*Orchitis* is the most frequent complication of mumps in young men and boys, occurring in 15 to 30 per cent. of the cases. Before puberty it is rare, but has been seen in infants. It develops at the end of the first or early in the second week; or, more rarely, before the parotid swelling. Severe prostration accompanies the orchitis, which may begin with a chill, and is often preceded by epididymitis. One side is more often affected than both. The symptoms last about one week, and the testes become normal in about two weeks. Atrophy results in about 53 per cent. of the patients affected. The incidence of orchitis is increased by previous testicular trauma or inflammation. *Oöphoritis* is less common in women than orchitis is in men. *Mastitis* may occur both in men and women.

Among the very rare complications of mumps are swelling of the labia majora; endocarditis, pericarditis, myocarditis; inflammation of the thymus gland; pancreatitis; appendicitis; arthritis; polyneuritis, and even quadriplegia; inflammation of the facial, acoustic, or optic nerves; iridocyclitis and disturbance of vision due to retinal congestion. Among the respiratory complications are bronchitis, pneumonia, and edema of the glottis.

Transient albuminuria during the febrile period sometimes appears. Later nephritis may develop and persist for weeks, with ultimate recovery. Death from uremia is rare.

Mumps meningitis, or *meningo-encephalitis*, has been observed in as many as 23 per cent. of cases in various epidemics, and affects children as well as adults. It may appear before the parotid gland is affected, though usually it comes during the height of the glandular lesion or after its resolution. The symptoms of meningitis may be mild or severe, but the average patient recovers in two to ten days. A fatal outcome is rare. Focal symptoms indicate encephalitis as well as meningitis. The spinal fluid is clear under high pressure, with an increase in lymphocytes and globulin; no film forms. Residual symptoms, like strabismus, lack of accommodation, deafness, aphasia, facial twitchings or paralysis, and hemiplegia, have been reported. All disappear either rapidly or after one or two years. At autopsy the meninges are turbid and edematous. On microscopic examination the lesion is one of edema and perivascular infiltration, with lymphocytes predominating.

Deafness may occur at any time during an attack or during convalescence. It may be sudden, complete, and permanent. The lesion is in the

labyrinth and more often unilateral than bilateral. Deafness occurs independently of meningitis, the parotitis virus apparently affecting the acoustic nerve directly.

Suppuration of the affected salivary glands is exceedingly rare and is due to preventable secondary infection.

Diagnosis.—During an epidemic the diagnosis of parotitis is easy. Differentiation from secondary parotitis requires a history of the primary infection, such as typhoid, scarlet fever, etc. *Cervical adenitis* can be differentiated by the location and character of the swelling and by the leukocyte count.

When the submaxillary or sublingual glands are involved without the parotids, the diagnosis can only be made with certainty if a history of exposure to mumps is obtained.

Prognosis.—In most cases the prognosis is excellent, especially in children. Complications which may end fatally are pneumonia, edema of the glottis, nephritis, and meningo-encephalitis. Blindness, deafness, or chronic nephritis are rare sequelæ.

The death rate during an epidemic in the American Army in 1918 was 0.33 per cent.

Treatment.—The prophylactic use of serum from convalescent mumps patients has been found effective when administered before the seventh day after exposure, in doses of 2 to 8 c.c. Therapeutically, larger doses are required (10 to 40 c.c.). The incidence of orchitis is apparently diminished by the use of the convalescent serum.

During the acute febrile stage *rest in bed* is essential. The incidence of complications is thereby diminished. Cleanliness of the mouth is necessary for the comfort of the patient and the prevention of suppuration of the inflamed glands. Kermorgant suggests the use of stovarsol or treparsol in the early stage of the disease. Local applications may be hot or cold. *Belladonna ointment* relieves the pain. For delayed resolution of the glands *potassium iodid* may be given. Orchitis requires cold applications and proper support, with rest in bed.

For prophylactic purposes mumps patients should be *strictly isolated* until all glandular swellings have disappeared. The quarantine should last two weeks in mild cases and as long as is indicated by persistence of symptoms in severe cases.

Exposed persons should be watched throughout the incubation period, or about three weeks. In schools and other institutions exposed and unexposed units should be kept strictly apart.

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PERTUSSIS

(*Whooping-cough*)

Definition.—Pertussis is a contagious disease which occurs throughout the year, but most frequently during winter. It is characterized by catarrh of the respiratory tract and coughing which occurs in paroxysms, each of which terminates in an inspiratory whoop. Baillou published the first account of the disease in Paris in 1578.

Incidence.—Age is the most definite predisposing influence. More than 20 per cent. of the cases occur in the first year and nearly 50 per cent. during the first two years of life. The susceptibility of children is extremely great and, on the whole, is quite comparable with that to measles, although in newborn infants and children less than six months of age it is far greater than to measles.

The disease may probably be transmitted by a third person. Phillips has reported 2 instances in which pertussis in the newborn was contracted from an obstetric nurse. One child began to cough on the tenth day and whooped on the fourteenth. One attack may confer lifelong immunity. Reports of second attacks in the same individual may generally be explained by errors in diagnosis.

Etiology.—Bordet and Gengou in 1906 described a very small, elliptical, Gram-negative bacillus which they found in the sputum in large numbers during the late catarrhal and early paroxysmal stages of the disease. Recent evidence confirms their opinion that this is specific. Klimenko and Fraenkel claimed they were able to produce typical pertussis in animals with this organism, but Wollstein could not confirm their experiments. The bacillus is most readily obtained from the plug of mucus coughed up after a paroxysm. During pertussis the *influenza bacillus* is usually present in the sputum, especially in the early stages, and is not infrequently found before the *Bordet-Gengou bacillus*. The relation of these two organisms in pertussis is very intimate. Clinically, influenza and pertussis are occasionally indistinguishable.

Morbid Anatomy.—A child may succumb to one of the complications of pertussis and yet show no lesions which may with certainty be attributed to the primary disease. Catarrhal inflammation of the respiratory mucosa, especially of the larynx and trachea, and to a less extent of the nose and pharynx, is probably the lesion most common in pertussis. If the disease

persists for any length of time before death there is usually some degree of pulmonary emphysema. Enlargement of the bronchial and tracheal glands, acute bronchiectasis, congestion of the brain and other organs are less commonly seen at autopsy.

Symptoms.—The *period of incubation* is variable and often difficult to determine. It is usually from five to fifteen days and averages about ten days. Pertussis is generally divided into three stages—the catarrhal, the paroxysmal or spasmodic, and the stage of decline. The symptoms of the *first stage* differ in no way from those of a mild attack of subacute tracheobronchitis, and usually excite no suspicion of pertussis unless there is an epidemic or a definite history of exposure. After about a week the cough, instead of showing a tendency to subside, increases in both frequency and intensity, until within a day or two the characteristic paroxysms occur.

In this *second stage* coughing is more frequent than at first, and each paroxysm is terminated by the inspiratory whoop which gives the name to the disease. The onset of a typical paroxysm can often be foretold. Explosive coughs recur in such rapid succession that there is no interval for the child to breathe; the face becomes congested and of a deep red or sometimes black color, the tongue protrudes, the eyes and the mouth discharge, and perspiration appears in the face; finally, the cough ceases and a long-drawn-out inspiration through the narrow glottis produces the curious sound called the whoop. A second paroxysm usually follows the first and sometimes a third and fourth occur in rapid succession. After the paroxysm a small amount of tenacious mucus is coughed up. This gives instant relief. Vomiting often occurs when paroxysms follow ingestion of food. Exhaustion of brief duration is produced by the severer paroxysms. Paroxysms are less frequent if the patient stays out doors, and are more frequent and severe at night. They may often be induced by the use of the tongue depressor, by deep palpation of the abdomen, by a full inspiration, or by close proximity to a child who is whooping.

All patients do not exhibit such typical symptoms as those described; many, indeed, cough for a number of weeks with only an occasional paroxysm, and vomit rarely or not at all. Such cases may escape recognition altogether and thus disseminate the infection. In robust young infants the disease may show the same manifestations as in older children, or there may be paroxysms of coughing without the whoop. In feeble infants the cough occurs frequently, is less intense, and the whoop may be replaced by the appearance of cyanosis or even by dangerous asphyxia which necessitates artificial respiration. In certain very young infants attacks of cyanosis may be the only symptom. The paroxysmal character of the disease may be considerably modified by intercurrent diseases, particularly by pneumonia.

The duration of this second stage is variable. Although it averages between three and six weeks, it may continue for a long time, or in very mild cases may stop after a single week.

During the *third stage* the frequency and intensity of the paroxysms gradually abate until the character of the disease differs in no way from ordinary bronchitis. The cough generally persists for two or three weeks, but during the winter and in feeble infants at any season it may be prolonged. Throughout the stage of decline the paroxysms may recur with the onset of any fresh respiratory infection, and for weeks or months after

all the symptoms of pertussis have vanished any respiratory infection may be a signal for the recurrence of the whoop.

Complications and Sequelæ.—The most serious complications of pertussis are, in the order of frequency, respiratory, vascular, and nutritional. *Bronchitis* can hardly be regarded as a complication because it develops in so many cases during the last two stages. It is more common during the winter months and in younger infants. *Bronchopneumonia* is the complication above all others to be dreaded, as it is so closely related to the high mortality in pertussis. It is particularly fatal in infants in the first few months of life, especially when it occurs in cold weather. *Atelectasis* in infants as a complication, and *emphysema* in older children and adults, both as a complication and a sequel, are very common.

Hemorrhage is produced mechanically by the passive venous congestion caused by the violent paroxysms. Bleeding takes place most frequently from the nose, but is also seen in the eye, where it is subconjunctival and sometimes so extensive that the entire sclera becomes blood red. Hemorrhages may also occur from the ears, the lungs, or into the skin. The most serious form is that within the cranium and is generally meningeal in nature. When severe it may cause death or leave paralysis of a type determined by the site and extent of the hemorrhage.

Nutritional disturbances are usually due to diarrhea and vomiting. The former is sometimes caused by excessive use of drugs, especially in infants and young children. Repeated vomiting often results in malnutrition which renders the patient more susceptible to other complications, particularly to bronchopneumonia. Convulsions, which are common in delicate patients when pertussis is severe, are the result of passive congestion of the brain. Infants and young children with latent tetany are particularly prone to convulsions during an attack of pertussis.

Otitis media is a frequent complication. It occurred in 7 per cent. of the 300 cases observed by Hermann and Bell. *Tracheobronchial adenitis* can hardly be called a complication, for it occurs with great regularity in severe cases, as is evidenced by autopsy findings. *Subcutaneous emphysema* of the neck and chest is one of the rarer complications.

Chronic intestinal indigestion is an occasional sequel to pertussis. *Tuberculosis* in some form not infrequently follows the disease.

Diagnosis.—In the paroxysmal stage diagnosis offers little difficulty. In the catarrhal stage it is rarely possible to make a diagnosis unless there has been a definite exposure or unless the disease is prevailing epidemically.

In a child who has not had the disease a persistent cough which tends to increase in intensity, is unaccompanied by fever or physical signs, and becomes worse at night, should be regarded as pertussis until its etiology can be determined. Enlarged tracheal or bronchial lymph-nodes, a foreign body in the air passages, influenza, and the thickened bronchial walls due to chronic bronchitis may give rise to a paroxysmal cough which occasionally simulates pertussis.

Usually there is marked lymphocytic leukocytosis with a decrease in the polymorphonuclear neutrophil count. The total white blood-cell count is usually over 15,000. It may, however, greatly exceed this figure and the percentage of lymphocytes may rise to between 65 and 75. These changes in the blood do not appear until late in the catarrhal stage; they become maximal at the height of the paroxysmal stage, and usually

do not disappear completely for a number of weeks. The disease is most contagious during the catarrhal stage. Intracutaneous tests have given no conclusive results as an aid to diagnosis.

Prognosis.—Age is the determining factor in prognosis; in infants under three months, in all delicate infants, and in those who are rachitic the outlook is always serious, particularly in winter. Fully two-thirds of the deaths from pertussis occur during the first year of life when the mortality is at least 25 per cent. Among children in institutions this figure is much higher. In New York State pertussis causes more deaths than scarlet fever.

Prophylaxis.—Pertussis is a highly contagious disease. Isolation and quarantine should continue for a period of at least six weeks. There are no known methods of preventing the development of pertussis after exposure.

Treatment.—The fact that so many different drugs have been advocated for the treatment of pertussis is presumptive evidence that none has any specific value. For the mild cases general care and the administration of a sedative at night to insure adequate sleep may be all that is necessary. Indiscriminate drugging should be avoided.

In warm weather patients of all ages are better when out-of-doors. In cold weather robust infants and older children, even though they have a moderate degree of bronchitis, have fewer paroxysms in the open air. Infants a few months old and delicate children are less subject to bronchopneumonia if kept indoors in bed. Paroxysms are always fewer when the patient is at rest. A snug abdominal binder adds to the comfort of the patient.

Older children who have vomited after a meal should be given another. If fluids are omitted at mealtime the tendency to vomit is minimized. Some children vomit less if food is given in small amounts at frequent intervals. Ingestion of liberal quantities of zwieback and dry toast with the meals also diminishes the tendency to vomit.

To prevent the vomiting of artifically fed infants the customary fluid formula should be replaced by milk and cereal mixtures boiled to the consistency of jelly. Such thick milk and starch foods may also be given in small amounts to nursing infants after feeding. They should be fed with a spoon.

Certain *drugs* which lessen the number of paroxysms prevent exhaustion and assure adequate sleep at night. Codein, antipyrin, belladonna, bromids, and chloral are the most effective of these. Antipyrin may be given without danger even to young infants; at three months of age as much as 1 grain may be given four or five times in twenty-four hours.

Inhalation of creosote and benzoin helps allay irritation and facilitates the expulsion of mucus. In certain severe cases a whiff of chloroform or hypodermic injection of morphin may be necessary to prevent asphyxial convulsions. O'Dwyer and Norton found it necessary to intubate in certain cases of glottic spasm. Bowditch and Leonard have treated pertussis by the Roentgen ray; their favorable results in certain cases were probably due to its effect on the enlarged tracheal and bronchial lymph-nodes. Such treatment cannot be recommended for general use. The conflicting reports of the value of intramuscular injection of ether seem to indicate that this form of medication has no advantage over those previously ad-

vocated. Goldbloom reports favorable results from the rectal administration of ether in olive oil (1 dram to the ounce). One-half ounce is injected twice daily.

Vaccines have been employed in recent years as a means of prophylaxis and treatment. Most of the reports of their alleged value cannot be accepted by the critical clinician, for conclusive evidence that vaccines made from the *Bordet-Gengou bacillus* have any specific value has not yet been obtained.

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SMALLPOX

(*Variola*)

Definition.—Smallpox is a specific infectious disease characterized by marked symptoms of invasion which subside with the appearance of a monomorphous eruption. The eruption passes successively through the stages of papule, vesicle, pustule, and crust. Frequently during pustulation there is a secondary fever and a return of the subjective symptoms.

History.—The history of smallpox dates far into antiquity. Some chroniclers believe there is evidence of its prevalence in China from 1122 to 249 B. C., or even earlier. Lesions on the skin of a mummy of the twentieth dynasty are presumptive evidence that it occurred in Egypt at this early date. India and Central Africa have, however, long been regarded as the native foci of the disease. The time of its introduction into Europe is not known, but unmistakable evidences of its prevalence during the early Christian era are to be found in the writings of an Alexandrian physician of the first century, of Herodotus and of Galen. Antoninus Pius is thought to have died of this disease. In an account by Marius of an epidemic in France and Italy (570 A. D.) the name *variola* appears for the first time. Ten years later Gregory of Tours described an epidemic that spread over southern Europe. The first clear description of the disease was written by Razes, an Arabian physician, during the tenth century ("De Variolis et Morbillis"). In the eleventh century the disease became prevalent in Europe, where it was doubtless spread by the crusades.

Smallpox first reached America in 1520 when a negro slave with the disease entered Mexico with the troops of Cortez. The epidemic, thus engendered, killed 3,500,000 people and exterminated whole tribes of Indians. The disease first appeared in Massachusetts in 1633, reaching Boston in 1649.

The term *variola* during the middle centuries included most of the acute exanthemata. *Morbilli* was clearly differentiated by physicians of the sixteenth century; *scarlet fever* (Febris scarlatina) was distinguished from morbilli by Sydenham in the seventeenth century; *rubella* recognized by deBergen in the eighteenth century; and *fourth* (*Dukes'*) *disease*, by Dukes, in the nineteenth century. This accounts for the appellations first, second, third, and fourth disease and, more recently, fifth and sixth disease, which are sometimes used.

The term "pox" comes from pocca, the Anglo-Saxon equivalent of variola. The epithets *small* in England and *petite* in France were added soon after the introduction of the grandpox (lues) into those countries in 1498.

Incidence.—Smallpox occurs throughout the world and has spread with the development of trade. The air-borne theory of the spread of the contagium which was at one time so widely accepted has, within quite recent years, given place to the more plausible contact theory. Justification for this change is to be found in the fact that it is now possible to care for smallpox patients in the same wards in which patients with measles, scarlet fever, and other contagious diseases are being treated with little or no fear of transmission when aseptic technic is employed. That this is possible without consideration of air currents leaves little doubt that direct or indirect contact is the greatest factor in the spread of the disease. Although individuals entering the small, crowded room of a smallpox patient frequently contract the disease—a fact that might be considered evidence of air-borne infection—it is very improbable that they do not touch some

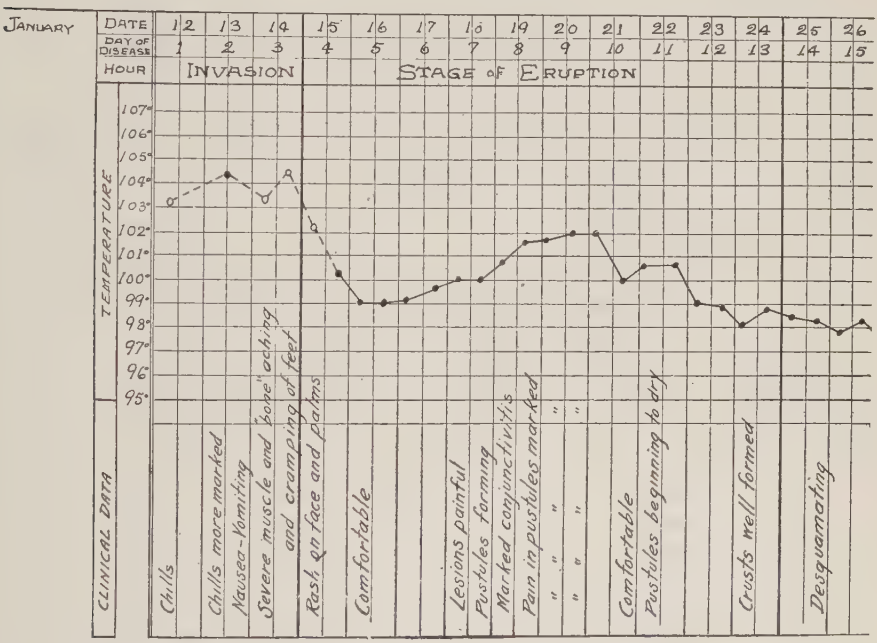

Fig. 6.—Typical temperature curve from a case of smallpox, illustrating the secondary rise.

infected article. Except within a radius of 3 feet air-borne infection is practically nil.

In olden times smallpox was a disease of the young because practically all adults had had it during childhood and were immune. Voltaire (1733) thought that at least 60 per cent. of persons were certain to contract the disease. Ben Jonson wrote, "Envious and foul disease, could there not be one beauty in an age and free from thee."

Age and Sex.—Variola is more commonly fatal in *infants* and *children*. A mother may infect the fetus, which may be born with the eruption at its height or in the crusting stage. *Sex* plays no part in the etiology.

Immunity.—While there are undoubted instances of natural immunity, it is rare. Permanent immunity, on the other hand, is acquired by a very large percentage of patients who recover from the disease. Two, three,

and even more attacks of smallpox have been said to occur in one individual. The validity of such reports, however, is seriously questioned.

Race.—The colored races, particularly the negro, are very much more susceptible than the white, and suffer more severely from the disease.

Season.—Recent, careful compilations show that smallpox is unquestionably a disease of the colder months. The incidence curve begins to rise in September, reaches its height in December and January, and then gradually falls, reaching its lowest limit during the hot months. The disease spreads most rapidly in crowded communities where the hygiene is bad. The natural resistance to certain infectious diseases (diphtheria) during the summer months may affect the incidence of smallpox. On the other hand, because of the great prevalence of smallpox in London during the summers of 1867 and 1869, Sydenham felt justified in concluding that the disease "ran an especially severe course in the high temperature of summer."

Severity of Epidemics.—Smallpox varies greatly in severity; a severe epidemic is frequently followed in succeeding years by epidemics of decreasing severity. Recently the prevalent type has been so mild as to cause, at times, much confusion in diagnosis, and has been considered a new disease called *Cuban itch, alastrum, milkpox, Philippine itch*, etc. Even in unvaccinated children, as well as adults, it may be mild or spurious. Jenner records an epidemic in Gloucestershire which was so mild that the people paid no attention to it and mingled together as usual in their ordinary daily occupations. They called it *white pox* or *swinepox*. No deaths occurred.

Etiology.—That a specific contagium or poison is the cause of smallpox has not been doubted for centuries. It is present in all stages of the disease, particularly in the vesicle, pustule, and crust, and probably also exists during invasion and the latter days of incubation. The contagium may cling to articles of clothing, blankets, and various objects for long periods of time. It is quite quickly destroyed by exposure to air and sunlight.

Guarnieri in 1892 showed that certain cell inclusions may be found in the proliferating epithelium of the vaccinated cornea of a rabbit. These he thought were produced by reaction of the tissue to the filtrable virus of the so-called dermotropic diseases (variola, vaccinia, and varicella). He called them *Cytoryctes variolæ*. They also appeared in the epithelial cells of the smallpox vesicles and in the vaccine vesicle—*Cytoryctes vaccinia*. Councilman and his co-workers found what they call a protozoön in the under layer of epithelial cells.

Over forty years ago Hirsch voiced a well-founded belief when he wrote, "Smallpox owes its origin to a specific poison that is capable of reproduction, and is therefore an organic body, and that it can at once exert its power in the form in which it is eliminated from the sick person, wherein it bears the clear mark of a contagious morbid poison—all this hardly requires to be proved, even though the investigations that have been directed to the detection of the poison have either had very doubtful results or no results at all." We have progressed but little further. Individuals have been inoculated with the disease by material from the lesion, from the exhalations, and by the blood of a patient; and monkeys have been successfully inoculated by the blood of smallpox patients. It has further been shown that the virus is filtrable, but its true nature, whether protozoön or bacterial, has yet to be determined.

Monkeys are quite susceptible to the disease. Bleyer records an epidemic of smallpox among the natives of the head waters of the Uruguay River which spread to monkeys of the region, decimating them. Dead monkeys found under trees were covered with pustules. In some regions certain species were exterminated. Anderson, of Glasgow, records a similar epidemic among monkeys in the forests of New Grenada which spread to the inhabitants of an adjacent town.

Morbid Anatomy.—The specific pathological changes are confined principally to the skin and mucous membranes. The *skin lesions* frequently develop more or less typically. The face and wrists are first involved, then the trunk and the extremities. The first manifestation is an erythematous spot or macule which quickly becomes a papule 2 to 3 mm. in diameter, slightly raised above the surface of the skin, of opaque reddish color, and definitely indurated.

Wigert (1871–72) described a peculiar lesion of the lowest layer of the epithelium in which the central cells of the papules undergo necrosis without disintegration of the necrotic material. He called this *diphtheroid degeneration.* The necrotic area forms the primary central focus of the pustule, but bears no relation to the development of the primary lesion. The rigidity of the cells, which develops early, is responsible for the peculiar dipping down or umbilication of the vesicle above the papule. Vesiculation of the epithelium, serous and purulent exudation, and reticulation produce the characteristic marked multilocular pock or pustule. If a vesicle be pricked with a needle, one compartment of the lesion is partially emptied. A cross-section of a lesion at this time may be likened to that of a poppy pod, with its central pillar and radiating partitions.

The presence of hairs and sweat glands at the point of umbilication is thought to account for the umbilication of some lesions. The exudation, at first clear, soon becomes cloudy. Cellular elements develop as it increases in quantity and ruptures the reticulum. Thus the characteristic yellowish green, well filled out umbilicated pustule is formed. This process may be superficial or deep, according to its localization in the epidermis or corium. Healing is accomplished by absorption, desiccation, regeneration of the epithelium, and desquamation of the crusts composed of cell detritus.

The *lesions on the mucous membranes* differ from those on the skin in that vesiculation and pustulation do not occur because of the absence of a horny epithelial layer. Accordingly, the necrotic or degenerated cells are soon cast off. Lesions appear in the mouth, trachea, conjunctivæ, and esophagus quite regularly; in the gastro-intestinal tube and vagina occasionally, and in the ureters or bladder, rarely.

In the protoplasm of the epithelial cells of the early lesion is contained the younger or cytoplasmic form of the so-called *cytoryctes variolæ*, while in the more advanced lesion the intranuclear form of the inclusion body is found.

Bacteriology.—Pyogenic streptococci are more numerous in the lesions of the mucous membrane than in any other disease, not excepting scarlet fever and diphtheria. Bacteria are generally absent from the vesicle and pustule on histological examination, but cultures and smears characteristically reveal the presence of a streptococcus during the pustular stage. Streptococcic septicemia usually develops in fatal cases.

Hemorrhage.—There are two types of hemorrhage, the diffuse hemor-

rhage into the corium which usually precedes the visible eruption and is almost invariably fatal (*purpura variolosa*) and the localized hemorrhage into the pock (*variola hæmorrhagica pustulosa*).

Lungs.—The most common and serious complications of smallpox are those of the respiratory system. Bronchitis, bronchopneumonia, and lobar pneumonia are thought by some to originate in a variolous lesion, but other observers do not see this relationship. The inflammatory exudate in the lungs contains large numbers of polymorphonuclear leukocytes. This is in marked contrast to the opposite condition in the skin lesions and in the other organs. The exudate may be hemorrhagic. The streptococcus and the pneumococcus are the predominating organisms.

Liver.—The liver is commonly enlarged, a change which occurs during the pustular stage and is quite characteristic. The normal adult liver weighs "1574 grams (Orth.), the typhoid liver 1894 grams, the liver in variola 2266 grams." The histological change is characterized by an infiltration with mononuclear basophilic elements, almost to the exclusion of polynuclears and is more marked in the interstitial tissues of the portal spaces. Large hemorrhagic foci are not infrequently found.

Spleen.—Moderate splenic enlargement is common during the pustular and crusting stages, particularly in children up to seven years of age. There is a very noticeable reduction in the number of polynuclear cells: frequently none are found except during the stage of desquamation, when the number may be increased. Many phagocytes which originate in the endothelial cells can be found and frequently are grouped together into distinct nodules in the follicles. They frequently contain the cytoryctes. Rarely and only in infants and children are nucleated red cells present. Hemorrhage into the spleen pulp is common.

Lymph-nodes.—The cervical lymph-nodes particularly are frequently enlarged, almost entirely by edema, which begins early and recedes with the disappearance of the eruption. Definite hyperplasia of basophilic cells, like those in the bone-marrow, takes place. This is particularly marked in children during the stage of vesiculation. Phagocytic cells are also found. During convalescence more polymorphonuclear cells are present in the sinuses than during any other infection except that with the streptococcus. Eosinophilic cells of the mononuclear type are more numerous than in other organs.

Bones.—*Osteomyelitis variolosa* of Chrari occurred in 86 per cent. of his 22 cases, being most marked in advanced cases. Mallory found the marrow affected in all the bones of the skeleton. In the suppurative stage colorless marrow cells predominate. Hemorrhagic smallpox increases the number of nucleated red cells. A marked reduction in the polymorphonuclear elements of the marrow is common and characteristic: there may be even complete absence of these cells, a condition not due to their degeneration in the marrow.

Other Organs.—More or less specific changes take place in the *kidneys*. Unruh, 1872, first called attention to hemorrhages into the pelvis of the kidneys and ureters. The bleeding is in and beneath the mucous membrane. Glomerular and epithelial changes are common. Councilman found nephritic lesions in all patients who came to autopsy, acute degeneration due to toxins, not to death, being the most common. The *adrenals*, *testes*, and *ovaries* are frequently involved more or less specifically so that symptoms

or clinical signs may develop. The *pancreas* is not involved. *Cardiac lesions* are unusual.

Symptoms.—Incubation.—The period of incubation lasts usually from eight to twelve days, but is known to have been as short as five days and as long as twenty-one.

Invasion.—The invasive stage continues for three or four days and terminates abruptly. The onset is sudden, marked by severe headache and a rise of temperature to 103° or 104° F. the first day and not uncommonly to 105° or 107° F. as the disease progresses. Chilliness or a definite chill in adults, and vomiting or a convulsion in children, are common. Severe headache and intense pain in the loins, lumbar regions, and extremities are more characteristic of smallpox than of any other disease of temperate climates except influenza. Not infrequently is the condition mistaken for *influenza*. In the South confusion with *dengue* must be considered. Even though the fever may be moderate and the subsequent course of the disease mild, aching is a prominent symptom. In the author's series 54 per cent. of the discrete cases and 66 per cent. of the varioloid cases had marked symptoms at onset.

As the fever continues, the subjective symptoms usually become exaggerated but without absolute sequential order of development. The *pulse* is usually full and of increased tension. Its frequency is not, as a rule, out of proportion to the fever (adults 100 to 103, children 150 to 160). The *skin* is usually hot. Sweating may occur and be profuse. The face is flushed, the eyes bright. At the height of the fever *restlessness* and *muttering delirium* often develop. In children, in addition to these common symptoms, drowsiness, sleepiness, and coma, which are rare in adults, are seen. *Prostration* is quite a prominent manifestation.

Initial Rashes.—A *scarlatiniform* and *morbilliform eruption* is seen in a small percentage of patients during the stage of invasion before the true eruption appears. These are sufficiently marked at times to cause confusion in diagnosis. They almost invariably develop on the second day of the disease and are not elevated above the surface of the skin, a fact which at once differentiates them from *measles*. This form of initial rash is said to be more common in varioloid smallpox. The comparative infrequency of the scarlatiniform rash and its varied and ephemeral nature are important means of differentiation from *scarlet fever*. A *petechial* or *hemorrhagic initial rash* composed of close-set, pin-point, purplish spots occasionally occurs. It is quite characteristically found over the lower abdomen, the inner aspects of the thighs, and the lateral thoracic regions. The rash may be, but is not always, the precursor of hemorrhagic smallpox.

The Eruption.—At first small dusky reddish erythematous spots develop 2 or 3 mm. in diameter. Within a few hours these become distinctly raised above the surface of the skin and gradually develop into true papules, about the end of the third or the beginning of the fourth day. The earlier the development of the eruption the more likely is it to become confluent. With the appearance of eruption the fever subsides and the patient becomes comfortable. Within a few hours the temperature may be normal.

The *papule* is distinctly firm, 2 to 4 mm. in diameter, and usually set well into the skin. This gives it the classic shotty character which, while not at all pathognomonic, is more characteristic of smallpox than of any

of the exanthematous fevers. The papule continues to develop in size until about the sixth day when it becomes capped with a multilocular *vesicle*. As the vesicle fills, the center becomes depressed or umbilicated. The clearness of the vesicle depends upon whether the lesion is situated superficially in the epidermis or not: if deep, it is often not recognized. The epidermal covering of the vesicle becomes opaque and the contents cloudy, until by the eighth day the *pustule* is well developed. This varies from 3 to 5 mm. in diameter, although single lesions are often much larger. They are elevated 2 mm. above the surface of the skin and have a very characteristic greenish- or grayish-yellow color. About the time of vesiculation a small area with a finely fringed edge develops about the lesions; this is a sign that allergy has been established. Thereafter, if variolous material is injected intradermally or rubbed into a scratch, a characteristic hyperemic allergic reaction results.

If the lesions are closely observed from day to day, they are seen to be, for the most part, in the same stage of development. As the eruption characteristically appears first on the face and wrists, and within a few hours on other parts of the body, one might easily find well-advanced papules on the face and young papules on the extremities. There is, however, no tendency for the mature lesions to develop into crops. The papules are all present the same day and vesiculation takes place in the same order. All the lesions then become pustular. In other words, in smallpox there is evidence of a true monomorphous eruption.

While these successive changes are characteristic of probably 90 per cent. of the lesions, some lesions will not pass through all the stages. Some may involute, while others progress very feebly through all stages. Not infrequently one in the midst of a group of active lesions is sluggish and, even though it may develop into a pustule, it may be no larger than a pinpoint and the whole lesion not more than 1 or 2 mm. in diameter.

When the lesions are distinctly separated from one another by clear spaces the condition is termed *discrete* or *distinct* smallpox; when they are so thickly set that they coalesce it is called *confluent* smallpox. The type is simply a matter of degree. In discrete smallpox there may be not more than five or six lesions scattered over the body or confined to a limited area (face or chest), or there may be very numerous lesions over the entire area of distribution. The confluent form, on the other hand, may be evidenced by distinct confluent lesions on the face with comparatively few on the rest of the body, or by confluent changes on the upper extremities as well. Union of the single points of eruption takes place during the stage of maturation to such an extent as at times to simulate a large superficial abscess.

It is in the confluent or severe form that marked congestion and edema cause complete disfigurement and a most distressing appearance of the face. The eyelids may be closed. The tenseness of the tissues produces much discomfort. The patient not only looks but feels wretched.

The *progressive development of the rash* is quite characteristic. Typically, the lesions start on the forehead at the hair line and the anterior surfaces of the wrists, then, in order, involve the face, upper extremities, and upper thorax. The abdomen, groins, and legs are the least affected. Lesions on the palms and plantar surfaces usually do not become vesicles or pustules, but dry and crust. *Pitting* is characteristic of confluent

smallpox. Sydenham said, "It is very rarely that distinct smallpox leaves its mark."

The Fever and General Symptoms During the Eruptive Period.—When the eruption appears the temperature quickly returns to normal or thereabouts. All subjective symptoms disappear and the patient feels well. When the vesicles develop the temperature typically begins to rise slightly, until the pustules form. At this time there develops the classical secondary or suppurative fever which gradually declines as desiccation begins about the twelfth day. In a mild case the discrete lesions may be so insignificant as to attract little attention and, as frequently occurs, no return of the fever gives warning that the disease is still continuing. In severe cases the initial symptoms return, but usually less markedly. In the mild form of variola, seen during the past few years, it is very common for no secondary fever or general symptoms to occur. In the writer's series of 121 cases of variola, all forms included, 85 per cent. showed no secondary rise in temperature; 68.7 per cent. of the 16 confluent, and 77 per cent. of the 9 varioloid cases showed no secondary fever.

Itching of the skin about the lesion is quite common. Great care must be taken to prevent scratching, particularly in children, for it almost invariably results in pitting. A disagreeable and somewhat characteristic *odor* is sometimes present during maturation.

Desquamation is quite variable. It may be well under way by the twelfth to the fourteenth day. In confluent smallpox lamellæ, or large crusts, are cast off. Sometimes a partial cast of a foot may come away. This is definitely thick as compared with the thin, sheet-like desquamation of scarlet fever. In the discrete disease a whitish, thin, circular desquamation may occur around the periphery of the lesion, separating from the inner side, or a scab corresponding to or a little smaller than the pustule may separate. There is no similarity between the desquamation of smallpox and that of scarlet fever or measles. A plum-colored discoloration frequently marks the site of the lesion and, although it may persist for some time, always disappears. A rather characteristic pigmentation of the skin is occasionally seen. Pitting almost invariably follows confluent smallpox. Occasionally a few pits follow discrete smallpox; they are rare in varioloid unless the lesions are irritated.

Mucous Membranes.—Painful stomatitis, salivation, and huskiness of the voice are the chief symptoms occasioned by lesions on the mucous membranes.

Glands.—Enlargement of the cervical glands or a general adenopathy is very frequent in both types of smallpox and may be quite marked. The epitrochlear glands may be involved.

The liver and spleen are frequently enlarged and palpable.

Types of Smallpox.—Hemorrhagic Smallpox.—Two types of hemorrhagic smallpox are well known—*purpura variolosa* and *purpura hæmorrhagica pustulosa*. The former is less common in children, develops before the eruption appears, and is characterized by hemorrhage into the skin and mucous membranes, from the kidneys, from the vagina, and sometimes from the gastro-intestinal tract. This type almost invariably causes death after from two to six days and is popularly known as *black smallpox*. *Purpura hæmorrhagica pustulosa*, as the name indicates, is hemorrhage into the pustule. The contents of the lesion changes from a greenish- or grayish-yellow

to a dusky blue or purple color. While this is an index that the disease is severe, it is not usually a sign that death will ensue. Certain patients with mild smallpox, if allowed to get up too soon, suffer hemorrhage into the pocks on the legs. Purpura variolosa is usually characterized by symptoms of great severity, but Gregory records an interesting observation, "In February, 1842 I saw a lady in smallpox whose whole body was the color of indigo and whom I at first believed to be a native of Africa. She conversed with me in the most tranquil manner and died a few hours later."

Blood.—Marked changes in the leukocyte count occur in many cases, especially during the stage of pustulation and secondary fever. There is a leukocytosis varying from 12,000 to 20,000. A differential count shows a preponderance of the mononuclear types, even in the milder cases when the leukocyte count may be within the normal range. A marked leukocytosis is characteristic of both hemorrhagic forms.

Varioloid.—Smallpox (*variola vera*), modified by vaccination, is called varioloid. If a patient who has been successfully vaccinated within five years develops mild or marked discrete smallpox, the disease is classed as varioloid. There are, however, unquestioned cases of modified smallpox in adults who have been successfully vaccinated in childhood. Varioloid is usually a comparatively mild disorder. Pitting rarely occurs if the lesion is not irritated. The initial symptoms may, however, be pronounced; a secondary fever is rare. Crusting takes place early. The involution of the lesions which occurs frequently renders differentiation from chickenpox difficult, as it suggests the appearance of a polymorphous eruption.

Abortive Types.—In the very mild smallpox seen recently in vaccinated or unvaccinated children and adults, abortion or involution of the eruption occurs occasionally. The eruption progresses to a certain stage, then stops, more commonly when the lesions are in the form of vesicles. The crusts are thin, yellowish, and somewhat crystalline or horny. In certain individuals who have been freely exposed and have the symptoms of the invasion stage, the eruption does not develop—*variola sine eruptione*.

Complications.—The most common and important complications are *laryngitis* which often produces serious edema, *bronchitis*, *bronchopneumonia*, and less frequently *lobar pneumonia* and *pleurisy*. *Delirium* is not infrequent during the febrile period. Trousseau pointed out many years ago "that *albuminuria* was almost as common in confluent smallpox as in scarlet fever." This statement is verified by Welch and Schamberg's statistics and by Arnaud's report of its presence in 95 per cent. of his 400 cases. The author has found albuminuria uncommon in discrete smallpox and frequently absent in the confluent form. The clinical manifestations of *nephritis*—edema, uremia, etc.—appear decidedly less often than in scarlet fever. Arnaud believes that structural, not functional alterations, are responsible for the presence of albumin.

Septicemia is not infrequent and is usually fatal. Councilman found the streptococcus constantly present in the blood. Kempton and Parsons have reported a case from the author's clinic in which the hemolytic streptococcus was present.

Less common complications and sequelæ are *otitis media* and *diarrhea* (especially in children), *confusional insanity*, *ataxic variolique*, *hemiplegia peripheral neuritis*, *bed-sores*, *gangrene*, and *subcutaneous abscesses*. *Boils* are a common sequela. *Blindness* frequently follows smallpox in countries

where vaccination is not systematically carried out. *Pustules* on the lid margin and *corneal ulcers* are common. The eyeball may be destroyed. *Arthritis* occasionally occurs during the later stages of the disease. A peculiar purulent arthritis which results in necrosis of the bone may occur in infants. *Pyelitis, abdominal pain, iritis,* and *hematoma of the ovary* have also been observed.

Prognosis.—In varioloid and discrete smallpox the prognosis is good, and depends largely upon the care the patient receives. In the epidemics of recent years even confluent smallpox has not been attended with the great mortality known in the prevaccination era. On the other hand, in the epidemic of 1924 many fatalities are recorded. In Detroit the 10 per cent. of cases which proved fatal were almost entirely among unprotected individuals. In the Philadelphia Municipal Hospital, of 4156 cases of variola, there were 1906 deaths (42 per cent.); while of 3048 cases of varioloid there were 31 deaths (1.1 per cent.). When the condition is associated with high secondary fever it is more likely to be fatal. Respiratory complications, particularly those of the lungs, must be considered grave. Any complication adds to the severity of the disease, and should, therefore, be carefully watched for and treated immediately. Probably in no other infectious disease is so much carelessness exhibited in the physical examination. The skin lesions seem to attract the most attention. Death is produced by visceral complications and septicemia.

Diagnosis.—The diagnosis of typical variola offers no difficulties, particularly during an epidemic. The distinct prodromal symptoms of aching, chill, vomiting and fever, their disappearance with the onset of the eruption, and the successive changes in the eruption, with or without the secondary fever, constitute an easily recognized syndrome. It is the mild, the modified, and the hemorrhagic forms that cause difficulty. In most such cases the initial symptoms remain characteristic, but they may be vague and be followed by the development of only a few lesions on the body which become involuted because of the influence of vaccination, and do not form pustules. A pustule should always excite suspicion. Any fever associated with the invasive symptoms of variola should be carefully watched.

The *malignant primary type of hemorrhagic variola* may easily be incorrectly diagnosed. The true variolous background of a septicemia may be overlooked until another member of the family or an exposed person develops true variola. During epidemics of influenza, scarlet fever, measles, and cerebrospinal meningitis, smallpox should be kept in mind. Septicemia which results in hemorrhage and endocarditis is not uncommon during their course.

The initial rashes may easily simulate those of *scarlet fever* and *measles*. The scarlatinal rash, being of short duration, rarely causes confusion. The morbilliform rash, however, may readily lead to error. The peculiar distribution of these rashes and the symptoms which precede and accompany them help in differentiation.

Chickenpox offers the greatest difficulty in differential diagnosis. Failure to recognize mild variola and its incorrect identification as chickenpox is a frequent cause of local epidemics. The polymorphous nature of the eruption of chickenpox and the monolocular character of the vesicle help in diagnosis, but are frequently deceptive. A pustular eruption, particularly

in adults, is very strong evidence of variola, and the history of a recent successful vaccination favors a diagnosis of chickenpox.

Measles may be confused with smallpox in the papular stage if only the lesions are considered. The first symptoms, the Koplik spots, and the continuance of the fever after the papules appear render diagnosis of measles easy. *Pustular syphilids* of the variolous type simulate variola so very closely, that in the absence of history and a positive Wassermann reaction they might be considered variola. Other lesions, like *impetigo contagiosa*, *pustular bromid eruptions*, and *pustular glanders*, have been mistaken for variola.

Laboratory Method of Diagnosis.—*Sensitization Test.*—For the sensitization test rabbits are sensitized to cowpox vaccine by successive injections. This requires about two weeks. The rabbit's belly is then shaved and a small amount of material from the vesicle or pustule inoculated intradermally. A positive reaction within twenty-four to forty-eight hours is indicative of smallpox. A rabbit remains sensitized for eight months.

Intradermal Cowpox Vaccine Test.—For the intradermal cowpox vaccine test cowpox vaccine (diluted 1 : 100) is heated to 56° C. A positive skin reaction follows intradermal injection of 0.1 c.c. of this substance if the patient has variola and has progressed far enough into the disease. If there has been previous vaccination, the test is of no significance.

Rabbit Eye Test.—If the cornea of a rabbit's eye is scarified with the corner of a cover-glass dipped in the contents of the variola vesicle or pustule, tiny "air blisters" may be seen within thirty-six hours with a hand lens and in forty-eight hours with the unaided eye. In three to four days epithelial necrosis occurs and ulcers form.

Prophylaxis.—Children should be vaccinated systematically in infancy, for a good "take" at this time unquestionably protects for many years. Revaccination is advisable when children enter the public schools, at about the sixth year. All individuals ought to be revaccinated during an epidemic if they have not been successfully vaccinated within three or four years. All those exposed should be promptly isolated and vaccinated. Vaccination during the incubation period may prevent the development of the disease. Enforcement of strict quarantine as early as possible is essential, and physicians should assist the health department in every possible way to secure information that will help stamp out the disease. The physician shields neither himself nor his patient by attempts to cover up the true nature of the disease.

Treatment.—Doubtless the low death rate of smallpox in recent years, particularly in hospitals, is due to improvement of the general treatment since the knowledge of hygiene and nursing has increased. Smallpox, like the other exanthemata, is a self-limited disease which, if uncomplicated, rarely causes death. Complications are most likely to begin during the early stages of the eruption when the patient may be unguarded because he feels well. Patients should be kept in bed until desquamation is complete. All personal and hospital hygienic measures must be carried out carefully. During the febrile period, on general principles, a light diet is best; later, the diet may be increased as the daily urinary findings indicate. The appearance of albumin is the signal for restriction of the protein (particularly animal protein) intake and the avoidance of an excess of salt.

Early Symptoms.—*Pains* are frequently relieved by the use of phenacetin. The smallest effective dose in an adult is 7 to 10 grains. Acetylsalicylic acid (10-grain doses) is very effective in some cases. Either of these remedies should be taken only when the physician observes their effects. Opium in the form of morphin is probably the most certain, and this is a legitimate time for its exhibition. A warm sponge bath is very comforting and often lowers the temperature; if not successful, cold water should be used. The nurse must be carefully protected.

Vomiting.—Washing of the stomach with large quantities of weak sodium bicarbonate solution may be all that is necessary to stop vomiting. Ingestion of a thick, smooth cereal with a small amount of milk often establishes normal downward peristalsis; half an hour later liquids, particularly water and clear tea, may be taken and retained. The common method of starvation and the swallowing of small bits of ice sometimes suffice, but it must be remembered that starvation, particularly when associated with fever, markedly disturbs the acid-base equilibrium toward the acid side. Severe "uncontrollable vomiting" is quite regularly controlled by the presence of glucose in the circulation. It may be administered by careful, slow, rectal injection (6 per cent. solution) or by very slow intravenous injection (50 c.c. of 20 per cent. sterile solution). Before glucose is given it is necessary that the patient take water or receive a saline infusion of 500 c.c. Every effort should be made to maintain the water intake. This alone, or particularly if combined with administration of glucose, may ward off vomiting.

Delirium.—Efforts to lower the fever either by phenacetin and acetylsalicylic acid or by bathing often relieve delirium. For that which follows the eruption morphin may be necessary.

The eruption tends to heal quickly. The lesions should be left undisturbed. The discomfort caused by tension does not last long, but if too unbearable may be relieved by small doses of morphin. Pitting results in spite of all efforts to prevent it, but is very frequently produced by mechanical disturbance of the lesions, such as scratching and rubbing against the pillow. Disfigurement may often be prevented by limiting the hand motion of the patient and by placing sand-bags at the sides of the head to hinder rolling to one side during sleep.

Itching is the most common and distressing symptom during the eruptive period. For this the simple calomine and zinc lotion is very effective medication; 2 per cent. phenol and weak solutions of bichlorid are beneficial. They also allay discomfort during the pustular stage and in many instances seem to limit the severity of the inflammation and the subsequent pitting. They should be applied on gauze or lint during the pustular stage when tension in the lesions is high. Phenol solution decreases the odor.

The Effect of Light.—A belief held for centuries that *bright light* favors the development of the papules seems to be confirmed by a remarkable instance in the writer's experience. One forearm of a patient was completely covered with the eruption while on the other there were comparatively few lesions. Investigation showed that while this patient was on the porch the arm covered with the eruption had been exposed to the sun and the other had not.

Finsen, who aims to exclude the actinic rays, has recently advocated

the use of red light. In a series of 300 patients treated in "red-light wards" by Brayton of Indianapolis the results were no different from those treated by ordinary measures.

Tincture of iodin painted over the lesions with a camel's hair brush is advocated by some to prevent swelling and to limit the development of the eruption.

Serum Treatment.—The serum of a recently vaccinated heifer was first used in the treatment of variola by Becterc, who reported favorable results. Welch and Schamberg, using smaller amounts, obtained no success in 6 patients. Convalescent serum has been tried by French clinicians without any marked beneficial results. This method of treatment is worthy of further trial in the light of results obtained with measles and scarlet fever. It may be found useful as a prophylactic measure.

Eye Conditions.—Great care must be taken to watch for eye complications. Instillation of argyrol (20 per cent. solution) should be started early, even if there are only a few lesions on the lid margin.

D. Murray Cowie.

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CHICKENPOX

(Varicella)

Definition.—Chickenpox is a specific infectious disease of childhood which is characterized by mild constitutional symptoms and a papulovesicular eruption that develops in crops.

History.—Ingrassias, a Sicilian physician, first differentiated the disease from smallpox in 1553, in a work entitled, "De tumoribus contra Naturam." To Morton is given the credit for introducing the name "chickenpox" into the medical literature, for he stated that the disease "was vulgarly known in this country (England) as chickenpox." "Varicella" was first used as a designation of the condition by Vogel in 1765. Heberden (1767) declared variola and varicella separate diseases and considered the latter due to a specific poison.

Etiology.—Chickenpox is a disease of childhood which sooner or later attacks a very large percentage of children. Those who escape frequently develop the disease in adult life, when it may be unusually severe. The cause of varicella is still unknown. The virus is contained in the contents of the vesicles, for the disease may be successfully transmitted by inocula-

tion of normal children with the contents of a young vesicle. The lesion is somewhat smaller than that of variola and is by no means as regularly induced as that of cowpox or smallpox by inoculation. Varicella is a so-called dermotropic disease and does not seem to be contagious during the first twelve days of incubation.

Incubation.—The length of incubation varies from four to twenty-seven days. Gregory says, "It does not exceed four days and is certainly less than seven." Trousseau considered it between fifteen and twenty-seven days, Osler ten to fifteen, Holt fourteen to sixteen. We have been so impressed with the regularity of the fourteen- to sixteen-day period in our wards that quarantine is omitted until the twelfth day after the patient is removed from the ward. *Quarantine* is then maintained for four days. If any cases develop, the subjects are promptly isolated and quarantine is again lifted.

Symptoms.—Invasion.—The invasive stage is short, not more than twenty-four hours. Usually in children the appearance of the eruption marks the beginning of the disease. In adults there are prodromal symptoms which, while not severe, lead the patient to seek medical advice. They consist of fever, headache, and aching. In varicella, however, there is not the clear-cut prodromal stage that is seen in variola, measles, or scarlet fever.

The eruption usually appears first on the trunk, then spreads to the face and the rest of the body. It is well marked on the scalp. A group of small, red, maculopapular spots develop and within twenty-four hours, often within twelve hours, become capped with clear, tear-drop vesicles. A narrow, red areola usually develops around the vesicle, the total diameter of which is 10 to 15 mm. In isolated lesions a large irregular rose-pink area (1 by 2 cm.) is not infrequently seen. The vesicle is round or oval, clear or pearly white in color, very superficially placed in the skin as compared with that of variola, and shows no constant, true umbilication. From new, well-selected vesicles freely pricked with a small (No. 1) darning needle, a clear fluid exudes and the lesion collapses, thus demonstrating its monolocular character. This is, however, not always demonstrable and should not be relied upon for diagnosis.

The vesicles develop in crops. The appearance of one group is followed within a few hours by the development of another, and still another, for three or four days. Consequently, at the height of the eruption all stages of development are visible simultaneously. This polymorphous character is of considerable value in differential diagnosis. Crusting occurs early because of the drying up of the vesicle and the formation of dark brown scabs, some of which may be very slowly detached. Scarring rarely ensues unless the pock has been injured. As the vesicle grows older the contents become turbid or even purulent. At times the purulent appearance of the eruption seems to result from the fact that the epithelial covering of the lesion becomes hydrated like a washerwoman's hands, for a clear fluid exudes if the lesion is punctured. An impetigenous lesion may form when a purulent vesicle ruptures; this spreads from the central crust and often covers an area 20 to 25 mm. in diameter.

The vesicle may be so small as to be almost invisible or so large as to be called *varicella bullosa*. Confluence, while rare, may occur on the face. A discrete eruption is, however, typical, and may be found on the mucous

membranes, the palms, and the feet. A preliminary *scarlatinal rash* has been observed. Holt reports 3 fatal cases of chickenpox resulting from erysipelas which originated about the pock. A fatal staphylococcic pyemic infection of a lesion is described by Bruner. Osler quotes descriptions of varicella "with cutaneous ecchymoses and bleeding from the mucous membranes." Renal complications occur, but are very infrequent. A relationship between varicella and herpes zoster has recently been suggested, but is by no means proved.

Blood.—Hoffman in 1923 observed 40 cases for twenty-seven days. The total leukocyte count varied little from normal. The differential count resembled that of variola, *i. e.*, there was a relative increase in the number of lymphocytes. The cosinophilic count was raised and myelocytes were present in the blood.

Diagnosis.—Although the diagnosis of chickenpox is usually not difficult, many blunders are made. The absence of symptoms or a mild onset, the appearance of successive crops of superficial vesicles, the absence of the greenish- or grayish-yellow pustule so characteristic of smallpox, the abundance of the eruption on the back and scalp, and the scarcity of lesions on the face are unmistakable evidences of varicella. In adults the prodromal symptoms may be as severe as in discrete smallpox or varioloid, but their duration is much shorter.

Prophylaxis.—For many years following the introduction of inoculation and cowpox vaccination, numerous attempts were made by eminent men to vaccinate against varicella by inoculating lymph taken from the vesicle at various stages of its development, but without any success. Some, however, succeeded sufficiently to advocate this as a practical protective measure. The author has been successful in producing the typical vaccinal lesions of chickenpox a number of times, but by no means as regularly as others report.

Treatment.—No special treatment is necessary. The disease is mild, self-limited, and, if ordinary hygienic measures are taken and the patient kept in bed, a good outcome is practically assured. The scabs often persist for many days and may need special attention. Itching is overcome by the usual measures (see smallpox). Children must be watched carefully to prevent scratching, as infection of the vesicle frequently results in a scar.

D. Murray Cowie.

VACCINIA

(*Vaccination*)

Definition.—Vaccinia is a specific infectious disease of the cow which was very prevalent in Gloucestershire, England, in the early part of the eighteenth century.

History.—It was quite generally known among the dairy folk that the disease was communicable to man, being manifested by vesicles, particularly on the inner upper aspect of the index-fingers and the back of the hands of milkmaids. There was a firm

belief that those who contracted cowpox could not take smallpox. Surgeons of the time, quite familiar with this tradition, gave it no serious thought, but the farm folk went so far as to test the efficacy of cowpox in preventing smallpox. In 1774 Benjamin Jetsy, a Yetminister farmer, inoculated his wife and children with matter taken from cows with cowpox. In seven or eight days vesicular lesions developed. Later the children were inoculated with smallpox virus and did not contract the disease. This information slumbered until seven years after Edward Jenner published his epoch-making work on vaccination.

Jenner, who was born in Gloucestershire in 1749, was much impressed by the tradition about smallpox. At the age of thirteen, while an apprentice to the eminent surgeons, Messers Ludlow, "a young country woman came to seek advice; the subject of smallpox was mentioned in her presence; she immediately observed, 'I cannot take that disease, for I have had cowpox.' This incident riveted the attention of Jenner" (Baron), and led him later to make a careful study of cowpox as it appeared in the cow so that he was able to detect the form of eruption that gave immunity. This he called true cowpox, the other types spurious cowpox. It was not until 1780, however, that he conceived the idea of general inoculation of material from cowpox lesions into man as a prophylactic measure against smallpox. Not until 1796 did Jenner actually begin to experiment with cowpox. He then took virus from the vesicles on the hands of a dairymaid, who had become inoculated with cowpox during milking, and inoculated it into the arm of James Phipps, a lad of eight years. Nineteen days later he inoculated the boy with smallpox virus. This experience started the great vaccination movement that spread all over the world.

Jenner soon prepared a very careful report of his work and sent it to the Royal Society for publication. It was declined on the ground that its publication might injure the credit Jenner had secured to himself in 1778 by winning the fellowship of the Royal Society "Chiefly through his admirable essay on the natural history of the cuckoo." He was forced to publish the paper himself in 1798 under the title, "An Inquiry into the Effects of the Variolæ Vaccinæ, a Disease Discovered by Some of the Western Counties of England, Particularly Gloucestershire, and Known by the Name of Cowpox."

In 1803 Parliament voted Dr. Jenner, as a reward for his discovery and service to the public, the sum of 10,000 pounds. Four years later this was increased to 30,000 pounds. Jenner was appointed physician extraordinary to the King of Great Britain in 1821, and died of apoplexy at Berkeley in 1823.

Vaccination was first performed in the United States by Dr. Benjamin Waterhouse, first professor of physic at Harvard. He was styled the "Jenner of America" by the unanimous vote of the London Medical Society. On July 8, 1800, he vaccinated his son, Daniel. The result being typical, he vaccinated five other members of his household. Two months later he sent his children to the smallpox hospital where they were freely exposed to the disease and inoculated with smallpox virus. They all resisted the disease.

Jenner believed until his death that cowpox and smallpox were simply different manifestations of the same disease. He accordingly called cowpox *variolæ vaccinæ*. He also demonstrated, as well as Loy and Sacco, that lymph taken from the vesicular lesions on the heels and legs of horses with a disease called *grease* produces vesicles identical with those of true cowpox when inoculated into a child. The fact that this material produced typical cowpox lesions when inoculated into cows was already known. In 1807 Gassner claimed to have produced smallpox lesions by inoculating smallpox virus into cows and stated that lymph taken from these produced, in man, lesions typical of cowpox vaccination. This observation was confirmed in 1839 by Creely who pointed out that it was easier to induce smallpox in the cow by inoculation of the mucous membrane of the vagina. Lymph taken from the resulting lesions had the same properties as that taken from true cowpox or grease lesions.

The belief is now quite general that smallpox, cowpox, and grease, or horsepox, are derived from a common source, and that each acquires certain characteristics by passing through the animal body. Jenner wrote, "The disease makes its progress from the horse to the nipple of the cow, and from the cow to the human subject."

Vaccine.—The first vaccine was prepared by dipping the point of a quill into lymph taken when the vesicle was young, before the area began to develop. Jenner wrote: "I do not care what British laws Americans discard, so that they stick to this—never to take the virus from a vaccine pustule for the purpose of inoculation after the efflorescence is formed around it. I wish this efflorescence to be considered as a sacred boundary over which the lancet should not pass." The virus was allowed to dry upon these quills and upon the "ivory" points which later became popular, so that it was easy and safe to ship it to the colonies. The French adopted the capillary tube. Later glycerin was used as a diluent and preservative.

To S. Monckton Copeman belongs the credit for placing the preparation of the glycerinated lymph used today on a scientific basis. Early lymph is very much more potent than that taken at the height of vesiculation.

Humanized Lymph.—Lymph taken from the early vesicle (fifth to seventh day) of a healthy child during a primary vaccination is called humanized lymph. It is quite potent, but not as much so as that from the cow.

The Course of Primary Vaccination.—The day of vaccination a slight redness (the traumic reaction) develops about the site of inoculation. This may persist for many hours, but usually fades at the end of twenty-four hours, so that on the second day little or no redness is visible. It is more marked in some individuals than in others. The *period of latency* which continues throughout the period of incubation begins with the disappearance of the first skin reaction.

The Papule.—About the fourth day an erythematous spot, 3 or 4 mm. in diameter, which is scarcely raised above the surface of the skin, makes its appearance. On the fifth day a true papule is formed which is more or less firm, deep pink or red, and hyperemic.

The Vesicle.—About the end of the fifth day, or the beginning of the sixth, a multilocular vesicle develops which gradually increases in size until the ninth or tenth day. At its height the lesion may measure 10 to 12 mm. or more in diameter, is considerably elevated above the skin surface, and shows distinct umbilication.

The character of the vesicle, as well as that of the scar, depends largely on the method of vaccination. If vaccine has been introduced into the cut of a clean knife a typical round or oval vesicle forms which is pearly white or yellowish and umbilicated at the center. If the skin is scarified or scratched, a procedure which favors exudation of fibrin and desquamation of cells, a crust forms and the very typical irregularly shaped vesicle develops about its periphery. The contents of the vesicle remains quite clear until the reaction has reached its height. Spontaneous rupture frequently occurs at this stage and a cloudy fluid exudes.

The Aula.—Just about the time formation of the vesicle is well under way a red erythematous areola forms about the periphery of the lesion with fringed edges which fade into the normal areas of the skin. This gradually increases in size for two or three days, is of a bright red color, and brings the total diameter of the lesion up to 15 or 20 mm. It is called the aula.

The Area.—On the eighth or ninth day a striking change takes place. A new zone of erythema develops with such rapidity that within twenty-four hours the diameter of the lesion may be 60 or 70 mm. and even finally encircle the arm. The color of this outer zone is lighter than the inner. As this process advances the cellular tissues become swollen, the axillary glands enlarged and tender, the temperature may rise to 103° F., and the patient may suffer from headache, nausea and vomiting, or chilliness. By the eleventh day the efflorescence has reached its height and defervescence begins. On the thirteenth or fourteenth day the redness, which has become dusky and lost most of its hyperemic character, has disappeared, leaving some discoloration of the skin, and a heavy crust to mark the site of vaccination.

The crust begins with local defervescence. Yellowish at first, it later becomes dark brown or blackish and quite thick. It gradually separates

at the periphery and finally, about the eighteenth or twentieth day, desquamates, leaving the characteristic scar with pitted and partitioned base. The scar, which may remain dark red or plum color for some time, slowly becomes paler than the surrounding skin. As years pass by, many scars which were quite marked become almost invisible.

Revaccination or Secondary Vaccination.—If additional vaccinations take place on successive days after a primary successful vaccination, all reach their height at about the same time. If a patient is revaccinated within four or five months of the primary vaccination, the incubation period is usually about one day or even less and an attenuated or modified lesion results. These secondary lesions, though *perfect*, are smaller. This is called the *immediate reaction*. When secondary vaccination follows primary vaccination after a long interval (six months to three or four years) the incubation period is shorter than at first, and the lesion reaches its height on the fifth or sixth day. The area, as a rule, is much less marked. This is called the *hastened reaction*. If revaccination has been properly performed and no papule develops, careful observation will generally reveal slight or marked erythema; a sensation of itchiness often develops after the traumatic reaction is over. This is a sensitization phenomenon. Jenner and the older writers recognized that these differences in the type of the vaccine lesion were influenced by their time relationship to the primary vaccination. "When the vaccine virus is reinserted on the fourth, fifth, or sixth day from the primary vaccination, the result is that the vesicles of the secondary vaccination form rapidly, and are hurried forward in their course so as to overtake the first crop, when the whole mature and scab together." "When revaccination is practised at distant periods from the primary insertion of the virus, the arm generally presents the appearance of modified cowpox, that is, the vesicles advance with abnormal rapidity. Areola forms around them on the fourth or fifth day. The resulting scabs are small and fall off in a few days. Much itching accompanies the process" (Gregory, 1851).

Revaccination should be performed when the child enters the public schools or about the sixth or seventh year, and during an epidemic. If no *take* occurs, it should be repeated. A large percentage of revaccinations take, but some individuals resist many attempts.

Technic of Vaccination.—At the insertion of the deltoid muscle the arm should be carefully cleansed with soap and water, and rinsed with sterile water. Antiseptics should not be used except when the skin is unclean. Great care should be taken to rinse or wipe off the antiseptic thoroughly with sterile water.

The method which produces the most perfect lesion, *i. e.*, the lesion free from the early central crust, involves the use of a very sharp knife. The skin is held tight around the arm with the left hand. With gentle pressure, one or two incisions about 1 inch long are then made through the epidermis down to the capillary layer. The drawing of blood has been forbidden by some writers because of the fear of washing away the lymph. Both our experience and that of many early vaccinators, however, tends to demonstrate that slight oozing of blood provides a more favorable base for vaccination. With this technic one or more typical vesicles are produced along the entire cut, like a streak culture on agar. Another procedure which prevents the development of a large lesion, and is painless, is to make two or three short cuts $\frac{1}{4}$ inch long and about $1\frac{1}{2}$ inches apart. In primary

vaccinations, if properly done, one of these almost invariably takes. The next best method, particularly when large numbers are being vaccinated, is to employ the cambric needle to make a few scratches, inducing a red surface. Scarifying by passing a scalpel quickly back and forth over the skin, with firm pressure until the superficial layer is removed and a shiny base with little red points is exposed, is a favorite method with some. Considerable serum usually exudes after such treatment and a crust forms which crowds the vesicle to its periphery.

Application of Vaccine.—Considerable lymph should be placed on the abraded surface and well rubbed in. The capillary tubes convenient for doing this must be kept from all contamination with great care. The lymph may be applied by piqûre, that is, by spreading vaccine on the skin and making ten or twelve punctures through it, each of which leaves a small amount of vaccine in the skin. Intradermal injection of 0.05 to 0.10 c.c. of lymph results in a successful take in a large percentage of trials. By this method the vaccine is held in the skin and the resulting lesion is somewhat modified. There is no danger in the use of living lymph by this method and there are some advantages. Chauveau vaccinated 6 children subcutaneously with living glycerinated lymph (0.02 to 0.04 gm.) in 1865. After the lymph is applied ample time should be given for thorough drying of the lesion.

Dressing.—A simple dressing made of a strip of sterile gauze 2 by 3 inches, fastened above and below with a strip of adhesive tape to form a sort of tent over the wound, is the best type of covering. This protects from dust and unclean clothing and permits observation of the progress of the lesion. When the lesion reaches its height and is about to burst, the dressing should be removed. It is still simpler to sew or pin a piece of sterile gauze inside the sleeve so that it covers the wound. If possible, the patient should be quiet during the height of the reaction, or the arm immobilized. Since vaccination is so important to the community as well as to the individual, careful technic and care should always be employed. Shields are sometimes harmful because of the ease with which they may be hit and thus bruise the wound. Sometimes this produces serious consequences. If the sterile dressing adheres to the lesion it is best not to attempt complete removal. The gauze may be trimmed close to the vesicle with sterile scissors and the reddened skin bathed with hot sterile saline solution. This frequently relieves soreness.

Complications.—Rarely, if a vaccination is conducted as above described, will serious *ulceration*, sloughing, and cellulitis occur. *Vesicular eruptions* and *erythema multiforme* may develop from the third day to maturity. Painful *enlargement of the axillary glands* is common during the formation of the area. General vaccinia and near pustules may develop about this time, and are an expression of hyperallergy. *Boils* occasionally occur.

Transmission of Disease by Vaccination.—*Tetanus* has been transmitted by infected vaccine. The present method of purifying vaccine by long exposure to the action of glycerin and careful culturing before use is a great safeguard. The tetanus bacillus is quite constantly present in the heifer's intestine and excreta. Comparatively few cases have been found and most of those were traced to a single source in Philadelphia (1901). *Tuberculosis* is rarely if ever transmitted by vaccination with cowpox

lymph, and is not reported to have followed the use of humanized lymph. With the latter *syphilis* may be transmitted, but even this is rare. The transmission of leprosy is questioned.

Contraindications to Vaccination.—During an epidemic of smallpox there are practically no contraindications to vaccination with the exception of the presence of some enfeebling disease. In a contagious hospital, should a case of smallpox develop, the other exanthemata are not contraindications to vaccination. The vaccination may be modified by these diseases.

When smallpox is not epidemic a favorable time may be chosen for vaccination. Infants should be vaccinated before dentition begins. The course of vaccination in an infant under one year is usually milder than in an older child. The child should be in good physical condition before vaccination is undertaken. Skin diseases which cause roughening or abrasion of the skin, such as eczema, impetigo, and discharging glands, are contraindications, as are also diarrhea and acute intestinal disturbances. Vaccination of tuberculous patients in an institution has been shown not to be hazardous.

Variations in the Course of Vaccination.—In a very small proportion of individuals vaccinia assumes the so-called mulberry or raspberry form. As the name implies, the lesion is a red to bright red, irregularly shaped excrescence elevated about 2 or 3 mm. above the surface of the skin. It is the same size or a little larger than the true vaccine vesicle. No area or constitutional symptoms accompany these changes in the author's experience. The surface of the mulberry-like divisions is smooth and inclined to be shiny. It looks not unlike a small vascular nevus. The course is prolonged. Such a reaction is not supposed to confer immunity, but is thought to result from a different virus carried from the cow in the vaccine. The vesicles sometimes rupture and become irritable quite early, exuding a clear lymph.

A false cowpox, described by French writers, is characterized by the development of a small dusky red or yellowish papule with a conical top on the first or second day after inoculation. This gradually increases in size until the fifth or sixth day, when it fades and dries up. Keloid develops in a certain percentage of vaccination scars, leaving a reddish elevated area, which at times becomes quite irritable. It persists for a long time, but disappears with *x*-ray treatment.

At the height of vaccination a group of small lesions may develop, which vary in diameter from 1 to 2 mm. and in number from 10 to 30. These are not due to infection or inoculation from the original lesion and have been seen to form when the original vesicle did not rupture. The so-called near pustules, which may number from one to four or five, are 3 or 4 mm. in diameter.

Generalized vaccinia is comparatively rare and is characterized by the development of small papules and vesicles (4 or 5 to 100) on various parts of the body. These secondary lesions develop in crops throughout a period of five or six weeks. Such an eruption must be distinguished from the secondary lesions due to auto-inoculation. Osler states that in children generalized vaccinia may prove fatal.

Roseola vaccinosa is an erythematous macular eruption of a wild rose color which develops when the vaccine lesion is at its height and may com-

pletely cover the body. Although it may be raised above the surface at some points, it usually is not. The macules, while at first glance suggestive of measles, are larger, flat, and have no characteristic arrangement.

These skin phenomena which occur during the height of the eruption are perhaps a manifestation of a state of hyperallergy. The ergin stimulated by the cowpox allergen and absorbed by the tissues reacts with the allergen still entering the body from the lesion. A similar and commoner eruption occurs in the course of variola (roseola variolosa). Revaccination occasionally excites the first vaccination, which did not take, to reaction, and the two may proceed and terminate together.

Blood Changes During Vaccination.—On the third or fourth day after vaccination the leukocyte count begins to rise, reaching its height (about 15,000) on the fifth day. With vesiculation there is a rather sudden drop in the count, so that by the eighth or ninth day, when the fever is at its height, there is distinct leukopenia. As the temperature falls the number of leukocytes increases and may remain slightly above normal for a few days. Leukopenia develops during the period of area formation.

In no country since the discovery of vaccination have as rigid sanitary measures been carried out as in England—notification, strict quarantine of patients and contacts, and careful disinfection. On the other hand, in Germany, where more attention has been paid to vaccination and revaccination, the death rate from smallpox has been much lower. From 1875 to 1905 England and Wales had 8342 deaths compared with 1115 in Germany (Schamberg). Vaccination and revaccination became compulsory by law in Germany in 1874. Since that time smallpox has ceased to be an epidemic disease. Unquestionably, vaccination and revaccination is the most important means of stamping out the disease.

General Leonard Wood records the experience of two battalions (700 U. S. soldiers) in Holguin, Cuba, in 1898: "A large number of American soldiers under a fair state of discipline was sent into a country infected with the most virulent type of smallpox, where the death rate was heavy and all sanitary conditions were against them, and although living for months in towns infected with the most malignant type of smallpox, to which they were constantly exposed, not a single case occurred in the regiment."

D. Murray Cowie.

TYPHUS FEVER

(War-fever, Ship-fever, Jail-fever, Prison-fever, Camp-fever, and Hospital-fever)

Sporadic mild cases occurring in New York were described by Nathan Brill, and in the eastern United States such cases are frequently called Brill's disease.

Definition.—Typhus fever is an acute infectious disease transmitted by the body louse; characterized clinically by sudden onset; continuous

high fever, terminating by rapid lysis after about fourteen days; a general macular eruption tending to become hemorrhagic over trunk and limbs, but avoiding the face; a delirium which may pass into a fatal coma, and a tracheobronchitis often followed by bronchopneumonia. Pathologically it is characterized by proliferative and thrombotic lesions of the blood-vessels of the skin, musculature, and central nervous system.

History and Distribution.—From the time of its recognition as an entity, by Frascastorius, early in the sixteenth century (De contagione et contagiosis morbis), typhus fever is known to have been one of the great epidemic diseases of the world, and, although occurring sporadically and endemically, it has been associated in history with a massing of persons in cities, prisons, ships, and camps. The presence of the virus, lice, and conditions favorable for the dissemination of lice, are the conditions which give rise to epidemics. Every great war has been attended with severe and terribly fatal epidemics except the Franco-Prussian War in 1870, and the Japanese-Russian War in 1907. During the recent World War typhus first came into prominence in Serbia in 1915. The German, Austrian, and Russian armies were severely attacked, as well as the civilian populations of these countries. The British, French, and American armies on the western front were free from the disease, a fact which can largely be attributed to the precautions of the Germans against introducing the disease from the East, for, once started, the disease would have run riot in all armies because of the prevalence of lousiness and the louse-borne trench fever.

Following the war there was a high incidence of the disease in eastern Europe, notably in Poland and Russia. Regions which are known to be important endemic centers of typhus are Central Europe, Russia, northern Africa, Ireland, Siberia, northern China, Indo-China, and Mexico. Australia and the West Indies are free. In South America the disease is endemic in northern Chile and Peru only, while in the United States and Canada outbreaks occur only when introduced by immigrants.

Without lousiness there can be no typhus, and throughout the world the peoples content with a state of lousiness are those afflicted by typhus, and it is upon these the responsibility for the maintenance of the virus rests.

Transmission.—While, experimentally, typhus has been transmitted by means of the head louse, the body louse only is of importance. There is no evidence that the virus of the disease is conveyed by sputum or excreta. The disease has been conveyed to man by a single louse in one feeding. The virus is probably introduced by the louse in the act of feeding, but whether by the salivary glands, esophagus, or by fecal soiling has not yet been determined. Arkwright and Bacot have shown that the virus survives in the excreta of infective lice at room temperature for eleven days. Infection of laboratory workers has occurred through the accidental spraying of infective material from lice into the eye, and there is some evidence that the virus in louse excreta can enter the body through slight abrasions of the skin.

There is a very conspicuous seasonal incidence with typhus fever. The disease is most prevalent toward the end of winter, and falls off rapidly with the coming of warm weather. The increase of clothing, with less frequent changes in the winter time, favors the multiplication of lice; while the crowding of persons in housing and sleeping quarters facilitates the trans-

mission of lice. No person can become heavily louse-infested who bathes and changes the underclothing once a week.

Etiology.—A number of different bacteria have been isolated and regarded as causes of typhus fever. All have been discarded. The organism now believed to be the cause of typhus, *Rickettsia prowazeki*, was first seen by Ricketts in 1910 in lice infected with Mexican typhus. These organisms were again seen by Hegler and von Prowazek in 1913 and were extensively studied by da Rocha-Lima and named by him in 1916. The presence of somewhat similar micro-organisms in non-infective lice and in lice infected with trench fever obscured the problem for a time, but it has now been proved that the organism acquired by lice when they feed upon typhus patients is a distinct micro-organism and is to be distinguished from all other micro-organisms by its morphology and intracellular location in the louse.

The League of Red Cross Societies' Commission to study typhus obtained very positive proof that *Rickettsia prowazeki* is the cause of typhus. This Commission proved that in infective lice the virus of typhus is not separable from *Rickettsia prowazeki*. They also demonstrated in the lesions of blood-vessels in man and animals identical micro-organisms. More recently, the work of Weigl, Bacot and Seegal, and Arkwright and Bacot has added further important proof, in that they have succeeded in causing *Rickettsia prowazeki* to develop in lice after the introduction of leukocytes and blood-platelets into the anus from typhus patients and from experimentally infected guinea-pigs. The still more recent work of Wolbach and Schlesinger showed that the virus of typhus may be propagated in tissue plasma cultures from infected guinea-pigs, and that even though the virus had been maintained for a period of nearly four years in guinea-pigs, micro-organisms indistinguishable from *Rickettsia prowazeki* appeared within cells in the tissue cultures. In spite of the failure to cultivate *Rickettsia prowazeki* in artificial culture-media, and hence to fulfil Koch's criteria, there is evidence, of equally conclusive character, that *Rickettsia prowazeki* is the cause of typhus fever. This is the constant occurrence of *Rickettsia prowazeki* in lice containing the virus of typhus fever; the inseparability of the virus and *Rickettsia prowazeki* in any kind of material, whether from lice, guinea-pigs, or man; the demonstration of *Rickettsia prowazeki* in lesions; and, finally, their appearance in tissue cultures after long maintenance of the disease in guinea-pigs.

Morbid Anatomy.—The gross pathology of typhus is not distinctive. Many patients die and show but little change at autopsy except the bronchopneumonia often responsible for or contributory to death. The *spleen* may be slightly enlarged before the second week; in the third week its size is within normal range. The *rash* is usually evident at the time of the autopsy because of its petechial character. *Skin necroses* or *gangrene* are occasionally found, and there may be symmetrical gangrene of the skin covering the extremities. *Thrombi* are rarely found in the large blood-vessels. The *central nervous system* rarely shows gross changes; occasionally there is noted a diffuse pinkish coloration of the cortex, with or without minute arachnoidal hemorrhages, suggesting the gross findings of encephalitis of whatever origin. The pathology of typhus is distinctly microscopical. *Proliferative lesions* of the small blood-vessels, arteries, veins, and precapillaries are found wherever the rash occurs and in the skeletal

muscles. The proliferative lesions are usually the site of mural thrombi, and occluding thrombi often occur and are responsible for the necroses of the skin seen during life. A distinctive perivascular infiltration occurs in the skin, producing the so-called "*typhus nodules*" of Fränkel. In doubtful cases excision of the skin is sometimes resorted to for purposes of microscopical diagnosis. Perivascular infiltrations and somewhat similar nodular formations may be found in a few other organs, notably the heart, while in the *central nervous system* the lesions are perhaps more abundant than anywhere else in the body, other than in the skin. In every *post-mortem examination* made by the writer in Warsaw in 1920, small lesions in surprising abundance were present in cerebrum, cerebellum, medulla, and the only portion of the spinal cord examined routinely, the upper portion of the cervical cord. These lesions are chiefly in the form of small tubercle-like lesions, proliferative in character, composed in large part of neuroglia cells and mononuclear cells of mesenchymal origin, macrophages. These lesions have been interpreted as being secondary to lesions of small blood-vessels and capillaries, which are identical in nature with those occurring in the skin. The blood-vessels of the pia and arachnoid are only occasionally, and those of the choroid plexus very rarely, involved. In addition to these proliferative lesions, which correspond in size to the various dimensions of miliary tubercles, there is a *perivascular infiltration* corresponding to that found in many forms of encephalitis. The distinctive typhus lesion, however, is proliferative in character and is unique. The number and wide distribution of the typhus lesions in the central nervous system may be considered to be the cause of the severe nervous symptoms which form so prominent a part of the disease.

Symptoms.—Prodromal Stage.—The period of incubation lasts from eight to twelve days. It is probable, however, that it may be more or less than this, because, according to the dosage, incubation in guinea-pigs may vary from five to twenty-one days. The onset is abrupt, although previous to this the patient may recall minor symptoms such as weakness, malaise, headache; while actual elevation of temperature has been observed a few days prior to the true onset.

Invasion.—As a rule, the invasion is abrupt, and accompanied by chills or rigor, followed by fever, from which the patient usually dates his illness. Vomiting may occur, but is infrequent. The appetite may be lost from the beginning, but this symptom is not constant. The prostration is such that the patient is glad to take to his bed. Neuromuscular and back pains are common, though less prominent than in influenza and smallpox. The fever is high, with pulse in proportion, and subject to considerable variation from hour to hour. The face is usually flushed, facies alert or anxious, mental condition excited, and active delirium may have begun. The pulse may be dicrotic, the spleen palpable, often tender. There is no glandular enlargement, lacrimation, or coryza. On the contrary, there may be slight dryness of the throat and tongue.

Stage of Eruption.—Eruption appears on the third to the seventh day, usually by the fifth day, in the form of round or oval, irregular, pink, erythematous macules which are non-palpable, disappear upon pressure, and appear at the base of the neck, chest, back, abdomen, and extremities. The individual macules are usually 2 to 5 mm. in diameter. In a few cases the macular eruption is complicated and partially obscured by a mottled

erythema which spares the face and is usually most pronounced on the chest, back, and arms. This erythema does not last more than three days and on disappearing leaves the macular eruption more clearly evident. Rarely large macules are distinctly palpable. The conjunctivæ at this stage of the eruption are markedly injected. The tongue in severe cases is dry and perhaps fissured. There is usually a cough, which by this time has become loose, and râles, sibilant and sonorous, are heard over the lungs. The eruption becomes more profuse, roughly in proportion to the severity of the disease, and in severe cases the lesions become almost confluent. At first light pink, they become deeper pink to bright purplish-red, and finally become brownish-red in appearance because of extravasation of blood, and on pressure remain a dull red. In severe cases more striking purplish-red petechiæ occur, sometimes of considerable size. Markedly hemorrhagic rashes may be accompanied by hematuria, hematemesis, and melena, and such cases are apt to be rapidly fatal. The fever is usually at its height from the fifth to the tenth day. More important, however, than

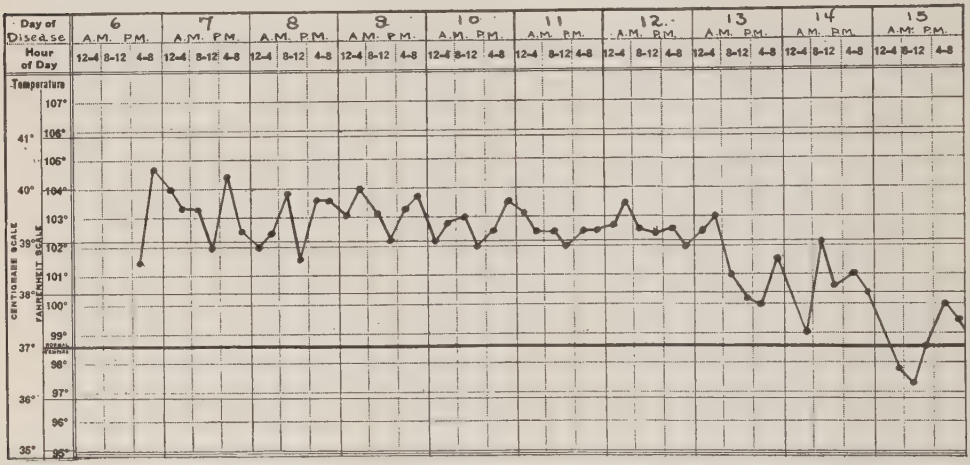

Fig. 7.—A typical temperature curve of uncomplicated typhus in a young patient who recovered.

the fever, in prognosis, is the severity of mental symptoms and complications. The temperature remains high, but somewhat irregular, until the tenth or twelfth day, when more marked remissions usually appear, with a rapid decrease to normal, on about the fourteenth day (Fig. 7). The pulse rate is more rapid than in typhoid, and a decrease may precede the fall in temperature. The mental and nervous symptoms are more striking than in any other acute general febrile disease, and in some cases there may be retraction of the head and other symptoms simulating cerebrospinal fever. The cerebrospinal fluid, however, shows but a slight increase in mononuclear cells and the fluid is not markedly turbid. Palfrey attaches great prognostic importance to the mental and nervous symptoms of the patient during the tenth to twelfth days. In some cases, in spite of a fall of temperature, the mental condition becomes worse, changing from delirium to coma, with carphologia, muscular twitchings, and incontinence of urine and feces. In these cases the rash remains profuse and becomes increasingly hemorrhagic. Such patients remain unconscious with increasing

exhaustion and emaciation in spite of normal or almost normal temperature for a period of a few days to a week, and die, usually with a terminal bronchopneumonia. In favorable cases, around the tenth or twelfth day a striking improvement occurs. Although still delirious, the patient becomes quieter, with an appearance of relaxation in spite of exhaustion. The flush of the face disappears, the pulse is less intense, the rash less evident, and the skin may be moist. The fever becomes remittent and, unless complications ensue, the temperature drops to normal within a few days.

The study of the Warsaw cases would indicate that relatively mild typhus infections may result fatally because of the severity of the complicating bronchopneumonia, while, on the other hand, severe typhus results in death because of the extensive involvement of the central nervous system. It has also been noted that in experimental animals the occasional deaths from typhus are those with unusually severe nervous lesions.

Clinical Pathology.—The *Weil-Felix agglutination reaction* is quite constant. For this purpose standard cultures of proteus-bacillus cultures must be employed. Those designated as "X-19" are used and are distributed in laboratories throughout the world. Living or dead emulsions may be employed and either the gross or microscopical technic used. The agglutination reaction does not appear until on or after the fourth day, and the highest titer is reached just before or just after the fall in temperature. The dilutions employed should be 1 : 25, 1 : 50, 1 : 100, and 1 : 200. If the result is positive in 1 : 200, greater dilutions may be used. It must be remembered that low dilutions, 1 : 25 or 1 : 50, may inhibit the reaction. The diagnostic value of the test is restricted by failure of agglutination to appear before the appearance of the rash, so it cannot be used early to exclude the presence of typhoid. In sporadic cases the reaction is of great value.

The *blood* shows no striking changes; the white count in uncomplicated cases rarely exceeds 12,000. Cases with marked leukocytosis are unfavorable. The *urine* shows changes common to other fevers. The *blood-pressure* remains strikingly low throughout the disease.

Complications and Sequelæ.—*Bronchitis* and *bronchopneumonia* are the outstanding complications of typhus, and the chief cause of mortality among the Warsaw cases was bronchopneumonia. The onset of pulmonary signs may be insidious or abrupt, and it is obvious that various types of infection of the lungs occur, chiefly streptococcus and pneumococcus. The great irregularity of the heart, with rapid and feeble pulse, and sometimes evidence of dilatation, may be taken as evidence of myocardial degeneration, which is often demonstrable at autopsy. On the other hand, with recovery, there are apparently no unfavorable after-effects in individuals who have exhibited marked cardiac signs. *Infections of the parotid and submaxillary glands* are not infrequent complications of typhus, and should be guarded against by careful cleansing of the mouth. *Gastro-intestinal* complications are of minor importance, and consist in vomiting and diarrhea. The latter is common during the height of the disease. The *delirium* and mental disturbance of typhus are to be regarded as a part of the disease rather than as complications. *Otitis media* occurs, as in other infectious diseases, with some frequency. *Thrombosis* of large arteries often causes serious complications. Peripheral, as well as abdominal vessels, are affected. In the Warsaw series there were cases of throm-

bosis of the mesenteric, carotid, pulmonary, and splenic arteries. Thrombosis of small cutaneous vessels results in the extraordinary necroses and gangrene of the skin so commonly observed in typhus epidemics. Previous impairment of circulation from pressure and cold is suspected as a predisposing cause, as the necroses are particularly apt to occur over bony prominences, such as the hips, sacrum, elbows, and scapulæ. The resulting sloughs may involve the underlying subcutaneous tissue and muscles. Symmetrical gangrene of the extremities has been also frequently noted in typhus.

Diagnosis.—Prior to the appearance of the rash, the signs and symptoms of typhus are so similar to many other *acute infectious diseases* as to make a differential diagnosis impossible, although in the presence of an epidemic the diagnosis may be made upon suspicion. The predominance of chill in typhus and of neuromuscular pains and coryza in other acute diseases is of assistance. *Malaria* and *relapsing fever* may be excluded by examination of the blood for the parasites. *Pneumonia* may cause confusion until characteristic pneumonic symptoms appear, such as accelerated respiration, rusty sputum, and the physical signs. *Meningitis* should seldom be mistaken, as meningeal symptoms occur only late in typhus. Lumbar puncture would eventually establish a diagnosis. In *measles* the coryza and lacrimation give a possibility of early distinction. *Smallpox*, while it may simulate typhus in the first four days, reveals itself later by the characteristic rash. *Scarlet fever* is distinguished by the character of the rash and other signs in the throat and on the tongue. *Typhoid fever* is so different from typhus in its mode of onset that the differential diagnosis is usually not difficult when a clear history can be obtained. Blood-cultures and Widal reactions may be resorted to. In the absence of history and in a late stage of the disease, there are some differences pointed out by Palfrey. The typhus patient is more apt to be excited, with active delirium and tense facies, in contrast to the more stuporous mental condition and relaxed facies of typhoid. The typhoid patient also lacks the injected conjunctivæ, and shows less flushing of the face. The rash in typhus is more profuse than in typhoid, and in the latter disease the rose-spots are usually palpable and do not become hemorrhagic. Skin excision may be resorted to. The enlarged spleen persists in typhoid. In recent years it has become necessary to differentiate *encephalitis lethargica* in countries where it coexists with typhus. The onset is usually gradual as contrasted with typhus, the temperature lower, rarely exceeding 102° F., and the period of fever short. There is no splenic enlargement and no eruption. *Rocky Mountain spotted fever*, if it should occur with typhus fever in the same community, could not be differentiated clinically. Rocky Mountain spotted fever needs only to be considered in the northwestern part of the United States where typhus is of great rarity. The history of exposure to ticks in an infected district would be of great assistance in differentiation. Absolute proof may be obtained only by means of guinea-pig inoculation, as there are striking lesions, particularly of the scrotum, and other evidence of severe illness in guinea-pigs infected with Rocky Mountain spotted fever, whereas the reaction of a guinea-pig inoculated with typhus can be determined only by means of the thermometer. There are no striking gross lesions. Finally, in addition to these tests, the cross-immunity tests would be available.

Prognosis.—The mortality of typhus in different epidemics has varied greatly, 50 and even 70 per cent. for one extreme, down to approximately 5 per cent. for the other. Factors such as ventilation, lack of attendance, food, and water, and even of beds have undoubtedly contributed to the high mortailty of the worst epidemics. There is a general feeling among the laity and physicians that the educated classes have a higher mortality. In childhood the disease is mild; in the second decade it is more severe, but death rarely occurs in individuals under twenty years of age. The mortality increases with the *age*. The liability to a severe bronchopneumonia becomes greater, and also persistent cerebral symptoms play a more important part. *Sex* is without influence except as affecting the physical condition and liability to alcoholism. The severity of the individual case can usually be estimated in the early stages by the degree of fever, profuseness of rash, and mental disturbance. Cases with severe symptoms in the early stages continue to run a severe course. A useful criterion of severity of the disease in all stages, according to Palfrey, is the presence or absence of dryness of the tongue.

Immunity.—It is not known whether a single attack confers immunity throughout life, although it apparently does in laboratory animals. It seems probable that the lower mortaility of the uneducated in typhus epidemics may be due to immunity acquired from attacks of the disease during infancy.

Prophylaxis.—Prophylactic measures in general may be summed up as those directed against lousiness. Persons attending patients should wear protective clothing, preferably a one-piece gown constructed with stocking footed trousers, with no orifices except at the neck and wrists. Close-fitting rubber gloves should be worn over the wrists, and the neck opening should be sprayed daily with an effective repellant, such as oil of cedarwood, or a solution of naphthalene. Nurses should wear, in addition, a head covering to confine the hair. The gown should be inspected frequently while being worn, and after each exposure should be deloused by heat, naphthalene, or chloroform. Heat is preferable—a temperature of 55° C. (131° F.) for fifteen minutes is sufficient. Bacot recommends the melting-point of stearin, about 60° C., as an indicator. Crude flaked naphthalene in a reasonably air-tight receptacle kills lice within ten or twelve hours. As soon as typhus is suspected, the patient should be freed from lice and nits and placed in a louse-free environment. His previous surroundings should be deloused and quarantined. In times of typhus epidemics it is wise to take precautions to prevent carriage of lice into the wards by ambulance drivers and other attendants. All blankets and clothing removed from the patient should be carried to a disinfesting chamber. The delousing of the patient should be superintended by an intelligent and trustworthy person. The patient should be clipped, with especial reference to head, axillæ, pubic and anal regions, bathed thoroughly, dried, and then sprayed or rubbed with a light oil, such as kerosene or liquid petrolatum. The head should be generously soused with this oil and tied up in a cloth for twelve hours. During epidemics, segregation and quarantine of contacts and immigrants from other typhus infected areas should be required for a period of sixteen days, in addition to delousing procedures. The methods employed by Strong in the Serbian epidemic were effective.

Treatment.—There is no specific treatment for typhus, and so far experiments with laboratory animals have given little indication of the success of either treatment or prophylactic inoculation. Treatment should be directed toward supporting the patient and eliminating as far as possible the sources of exhaustion until spontaneous recovery can occur. Continuous rest in bed and nursing are most essential. An abundant diet of soft solids should be given according to appetite and digestion. Liquids should be given frequently and in abundance. Every effort should be made to combat the dryness of the mouth and to keep the oral cavity clean; it is advisable to apply a cleansing solution every few hours. Where necessary, in delirious or comatose patients, nasal or esophageal tube feeding should be resorted to. Bathing should be practised as in typhoid. The bowels should be kept open with enemas and retention of urine should be guarded against. Headache should be treated with an ice-bag. Antipyretics are to be permitted only when the headache is out of proportion to the severity of the general condition. For the exhausting insomnia, veronal or chloral, and for the more violent delirium, hyoscin hypodermically, with or without morphin, should be given with the idea of conserving the strength of the patient. The cough, if exhausting, should be treated by the usual cough mixtures, with the addition of sedatives. The onset of pneumonia requires additional efforts toward diminishing the exhausting effects of restlessness, excitement, and cough. Small hypodermic doses of morphin proved useful in Warsaw. The possibility of skin necroses and gangrene should be kept in mind. The employment of pads to avoid pressure from bed-clothing and frequent changes of position should be instituted upon the slightest indication of these complications. There should be constant supervision of typhus patients in order to guard against accidents in delirium. After recovery, the effects of nervous and mental exhaustion may persist for some time and should be taken into account before the patient is permitted to resume normal activities.

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ROCKY MOUNTAIN SPOTTED FEVER

(*Black Fever, Blue Disease, Tick Fever*)

Definition.—Rocky Mountain spotted fever is an acute specific infectious endangeitis, chiefly of the peripheral blood-vessels, transmitted by a tick, *Dermacentor andersoni* (*venustus*), and characterized by onset with chills; continued fever terminating in lysis; severe pains in bones and muscles; headache; and a macular eruption, becoming petechial, which appears first on wrists, ankles, and back, and then over the whole surface of the body.

History.—The disease has probably existed in Idaho and Montana since the first settlement by white men, and seems to have been known to the Indians before that time. It was first described by Surgeon Major W. W. Wood, in 1896, in a report to the Surgeon-General. Maxey, of Idaho, and McCullough, of Montana, gave the earliest clinical descriptions of the disease. Important laboratory and field investigations were made by Wilson and Chowning, and Ricketts and his associates. Ricketts established the transmission of the disease by the tick, and defined most of the problems which have resulted in our present knowledge of the disease and its causation.

Distribution and Incidence.—The distribution of the disease is that of its carrier, the wood-tick *Dermacentor andersoni* (*venustus*), which is found in Idaho, Montana, Utah, Wyoming, Nevada, Oregon, Washington, Colorado, California, New Mexico, and South Dakota. The distribution of the disease is probably spreading. Its appearance in the various states is strikingly limited to discrete localities; for instance, in Idaho, where most of the cases occur in certain counties in the Snake River Valley; while in Montana the disease for a long time was restricted to the west side of the Bitter Root Valley, but since 1915 has appeared in localities in eastern Montana. The disease occurs almost wholly in the spring months after the melting of the snows, and lasts throughout the period of activity of the ticks, *i. e.*, from March until July. A few cases have been reported as late as October.

Transmission and Etiology.—The disease may be communicated to monkeys, rabbits, and guinea-pigs. White rats and mice are not susceptible. Infected ticks have been recovered from rodents in the Bitter Root Mountains and foothills and from the Rocky Mountain goat. The sole method of transmission in nature is through the feeding of ticks. Animals cannot be infected by contact and no instance of contact transmission of man is known. In the natural transmission, but one species of tick is concerned, *Dermacentor andersoni* (*venustus*), although in the laboratory other species of *Dermacentor* have carried the infection, and recently Parker has shown that the rabbit tick, *Hemaphysalis leporis-palustris*, can transmit the infection. The organism which was seen and described by Ricketts as a bacterium, resembling the plague bacillus, and which he observed in the blood of patients and in ticks, has been conclusively proved to be the cause of the disease by the work of Wolbach. The micro-organism is now generally classed with the poorly defined group of *Rickettsia*, and does have many resemblances to the cause of typhus fever, *Rickettsia prowazeki*. It is a minute bacterium-like micro-organism which does not stain with aqueous solutions of ordinary dyestuffs. Giemsa's stain is best for its demonstration. In the tick the organism undergoes a definite morphological sequence; in man and pathogenic animals it occurs constantly in the lesions of the disease, an observation which has been confirmed by Nicholson. It has not been cultivated on artificial media. The organism develops in tissue plasma cultures within cells of endothelial origin. Such cultures remain virulent for labora-

tory animals. While this micro-organism, named by Wolbach *Dermacentroxenus rickettsi*, bears many resemblances to the pathogenic rickettsias of typhus and other non-pathogenic rickettsias, it seems advisable to let the name stand until our knowledge of rickettsias is more complete. The organism in the tick is transmitted from generation to generation, and hence the maintenance of the disease is independent of human and possibly animal passage. In the tick, as in the mammalian body, it is always intracellular, which seems to be a characteristic of rickettsias in general. It is extremely susceptible to physical and chemical agents, although it does survive in the frozen and desiccated state for a considerable period of time.

Morbid Anatomy.—The study of Rocky Mountain spotted fever has been greatly facilitated by the fact that the disease is exactly duplicated in laboratory animals (monkeys, rabbits, and guinea-pigs) in respect to its general course and the distribution and character of the lesions. The pathology of the disease resembles in many respects that of typhus. The distinctive gross lesions are those resulting from the thrombosis of blood-vessels. In the male there is frequently extensive hemorrhage and necrosis in the tissues of the scrotum. There also may be necroses of the skin of the ears, face, fingers, toes, and vulva. The spleen in man and animals is enlarged to several times the normal size; it is firm and dark red. Gross changes in the other organs of the body are essentially lacking. The blood is dark red and clots slowly. The right side of the heart is commonly dilated, but the myocardium shows no change. The lungs are normal unless there has been secondary pneumonia. The gastro-intestinal tract, pancreas, liver, the adrenal glands, and kidneys show no gross lesions. In spite of the hemorrhagic lesions of the testes and ovaries, the bladder, prostate, and uterus show no lesions. In cases of long duration the marrow of the long bones becomes red because of resumption of activity. The blood-vessel lesions consist at first of a proliferative reaction of the endothelium, followed by thrombosis, either mural or occluding. A considerable degree of perivascular infiltration occurs, but the perivascular nodules so distinctive of typhus do not develop. Again, in contrast to typhus, the central nervous system escapes lesions. The parasite of the disease is found in endothelial cells and also in smooth muscle cells of blood-vessel walls. Arteries, veins, and capillaries are affected.

The clinical laboratory findings are not impressive. The urine is that of any febrile disease. In uncomplicated cases there is a slight leukocytosis, not above 12,000. There is an increase in the large mononuclear leukocytes, exclusive of lymphocytes, and presumably leukocytes of endothelial origin. The red cells decrease in number as the disease progresses and may fall below 3,500,000. Eosinophils are decreased and may be entirely absent.

Symptoms.—Incubation.—The disease in most cases in man probably develops between the fourth and eighth day after the feeding of the tick. The extremes reported have been two and twelve days. In two experiments upon humans, in which the disease was transmitted by a tick, the incubation period was three to nine days.

Prodromal Stage.—Before the definite onset of the disease there may be a few days of malaise, accompanied by chilly sensations and loss of appetite. This prodromal stage is more common in Idaho, where the disease is less severe than in Montana. The *onset* is usually accompanied by a chill, and there are severe general pains referred to the bones, muscles, back, and

joints, particularly in the calf muscles, large joints, and lumbar region of the back. Headache is common and severe. The face is flushed, the conjunctivæ injected, and the tongue white-coated, with moist edges and tip. Constipation is usual. There is usually photophobia and there may be epistaxis. A short dry cough is common. The patient is frequently ill enough to take to bed on the second day of symptoms.

Temperature.—Before the initial chill there may be slight evening elevation of temperature. Following the chill the temperature rises fairly rapidly and reaches 102° to 104° F. (38.8°–40° C.) by the second day. It continues to rise gradually to a maximum of 104° to 105° F. (40°–40.5° C.) during the second week. In very severe cases in the Bitter Root Valley temperatures from 106° to 107° F. have been recorded. The maximum temperature persists during the second week of the disease, with slight morning drops. With recovery, the temperature begins to fall at about the end of the second week, continuing by lysis, so that normal temperature is reached at about the end of the third week. After recovery the temperature may be slightly subnormal for a few days. In fatal cases the temperature may drop to normal or subnormal and then rise eighteen to twenty-four hours before death, which in severe cases usually takes place between the sixth and twelfth days of the disease.

The *pulse* is at first full and strong, but gradually loses volume and strength, and increases in rapidity out of proportion to the fever. The pulse rate ranges from 110 to 140, and may reach 150 a few days before death. A pulse rate of 120 with a temperature of 102° F. is not uncommon.

The *respirations* behave very much as does the pulse. They are rapid and out of proportion to the apparent severity of the illness, usually 30 to 40 a minute, but increasing as high as 60 before death.

The *rash* appears usually on the third, fourth, or fifth day of fever, most often on the third; occasionally as early as the second or as late as the seventh day. It appears first on the wrists, ankles, and back, then on the forehead, arms, legs, chest, and abdomen. The efflorescence requires twenty-four to thirty-six hours, although the eruption may appear still later than this on the palms of the hands, soles of the feet, and scalp. The mucosa of the cheeks, palate, fauces, and pharynx may show the eruption. The temperature is not appreciably affected at the time of the eruption, but the subjective symptoms ameliorate. The rash at first is in the form of rose-colored macules 1 to 4 or 5 mm. in diameter, not elevated, not palpable, and disappearing upon pressure. The skin may be tender at the site of the spots. The macules soon become deep red or purplish in color and increase in size, often becoming confluent. After a few days the rash begins to persist upon pressure, and then becomes generally petechial in character. Cutaneous and subcutaneous hemorrhages of considerable size occur frequently in severe cases, and the skin in the second week of the disease may assume a glazed appearance. Where the skin is thin, as over the thighs, a peculiar dusky reddish or bluish mottling may often be seen, which is due to stasis of blood in the subcutaneous vessels because of thrombosis. In mild cases the rash does not become confluent, and the petechiæ, remaining small, give a peculiar mottling which several Idaho physicians have compared to the markings of turkeys' eggs. Slight icterus may appear in the second week of the disease. The rash begins to disappear with the subsidence of fever, but may long be indicated by the persistence of pigmented spots.

Necroses of the skin of the scrotum, prepuce, fingers, toes, vulva, lobes of the ear, and mucous membrane of the soft palate may occur in the third week. *Desquamation* follows recovery, but is slight except where the lesions have been most marked. Minute cicatrices in the skin may persist for a long time after recovery.

Nervous Symptoms.—Restlessness and insomnia are very common throughout the disease and constitute its most distressing features. Hyperesthesia may be severe. Delirium is usual in severe cases during the height of the fever, and coma usually precedes death by a few hours or a day. Rarely convulsions, muscular rigidity, and opisthotonus occur.

Complications.—Pneumonia is the one complication, and is not frequent.

Diagnosis.—Theoretically the same diseases must be considered in the differential diagnosis of Rocky Mountain spotted fever as in typhus, but practically the seasonal incidence and restricted distribution of the disease eliminate a number of possibilities. *Cerebrospinal fever* and *measles* are the two diseases most liable to be temporarily mistaken for Rocky Mountain spotted fever. In cases of doubt, spinal puncture should be resorted to when there is a question of cerebrospinal fever, as the rash may simulate that of Rocky Mountain spotted fever. Usually the more severe nervous symptoms with early rigidity of the neck and character of the onset should serve to differentiate the two. Measles at its height in children presents difficulty, as the rash may resemble the early rash of spotted fever very closely. The history of slower onset, with coryza and lacrimation, the presence of Koplik's spots, the absence of severe muscular pains, and the papular character and sequence of distribution of the rash are the most important differential data. Typhoid fever, with a pronounced rash, may also have to be excluded. The rash in typhoid fever, however, is more palpable and elevated than in Rocky Mountain spotted fever, and is generally more restricted to the trunk. A slower pulse rate, lower fever, diarrhea, and positive blood-cultures, or a positive Widal make final exclusion easy.

Prognosis.—The severity of the rash in Rocky Mountain spotted fever is without prognostic importance. Patients with severe nervous symptoms are to be regarded as gravely affected. The critical period in the disease is toward the end of the second week, and the pulse and respiration rates furnish the best guide in regard to the severity of the case. A sudden increase in the white count, as indicative of a secondary infection, usually means a fatal termination. The mortality rate varies markedly in different regions. In Idaho the mortality is in the neighborhood of 3.5 per cent., in the Bitter Root Valley it approximates 90 per cent., while in eastern Montana it is about 15 per cent. As in typhus fever, the mortality in young children is insignificant. As a rule, the danger increases with the age of the individual.

Prophylaxis.—The wood tick, *Dermacentor andersoni* (*venustus*), does not inhabit dwellings, nor does it remain attached to its host after engorgement. Its active period is from the first warm days in spring, that is, early in March, to the end of June or first week in July, when it goes into retirement. The general measures to control the disease are directed toward the reduction of numbers and the limitation of distribution of ticks. The two methods of greatest practicability, and which have met with some success in the Bitter Root Valley, are the destruction of the small mammals which act

as hosts to the larvæ and nymphs, and the dipping of cattle infested with adult ticks. Clearing and cultivation of the land have made regions safe that were formerly unsafe. Lands unfit for agriculture promise to remain sources of infection unless the ticks can be controlled by new methods. Brumpt's suggestion, the introduction and acclimatization of hymenopterous insects (Ixodiphagus) which are parasitic upon various genera of ticks, should be tried. Personal prophylaxis means the avoidance of tick bites. This is not difficult for the casual traveler, but is very difficult for those who work in tick-infested regions. A protective one-piece working costume may be improvised by sewing trousers and shirt together. The trousers should be worn inside heavy woolen socks with high laced boots. It is also advisable to interpose a strip of greased felt or other absorbent material in the neck band and wrists. Stripping and inspecting the body for ticks would greatly diminish the chances of contracting the disease, as the tick is slow to attach and ordinarily remains attached for a short period before beginning the act of feeding. Spencer and Parker have obtained promising results with a vaccine consisting of phenolized emulsions of the organs of infected ticks. The vaccine will protect laboratory animals, including monkeys, against the disease and, therefore, its use should be encouraged as a means of protecting individuals exposed to Rocky Mountain spotted fever.

Treatment.—There is no specific treatment. The measures to be used are those employed in other continued fevers. Bathing may be employed to reduce temperature in the absence of hyperesthesia. Antipyretic drugs should be avoided. Hypnotics, such as morphin and hyoscin, may be recommended when the hyperesthesia, restlessness, and insomnia become of importance in the production of exhaustion. All efforts should be directed toward keeping up the strength of the patient, and hence the diet should be nutritious, liberal, and easily digestible, particularly during the first stages of the disease. Liquids should be given in abundance, and a daily movement of the bowels secured by enemata or aperients. Digitalis may probably be used to advantage, as in pneumonia; a few doses should be given at the onset of the disease in order to digitalize the heart, and should be followed by others when the pulse rate becomes unduly high. Drugs which have been employed without benefit are quinin, coal-tar products, calcium sulphid, creosote, sodium citrate injections, and various forms of arsenic, including atoxyl, salvarsan, and sodium cacodylate. Salvarsan and atoxyl are decidedly deleterious in their effect. On theoretical grounds the transfusion of blood from an immune donor should be tried when opportunity occurs in the early stages of the disease.

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TRENCH FEVER

(Trench Fever, Volhynian Fever, Quintan or Five-day Fever, Polish Fever, Russian Intermittent Fever, Meuse Fever, His-Werner Disease, Gaiter-pain Fever, Shin Fever, Shank Fever)

Definition.—Trench fever is a persistent acute infectious disease, characterized by recurrence of brief attacks of fever, severe pain in the muscles and bones, great prostration, enlargement of the spleen, and a rash.

Occurrence.—Since trench fever is transmitted by the louse, it may occur in any unclean, densely populated region. It most often attacks troops in active warfare, but also develops in civil communities in which conditions are suitable for the spread of louse-borne diseases. One-third of all the sickness in the British Army during the Great War is thought to have been caused by trench fever; and Grierson states that at one time 60 per cent. of all the patients in the British military hospitals had this disease. There seems to be little or no natural resistance to the infection; and immunity is not conferred by previous attacks. Healthy individuals are as subject to trench fever as those whose vitality has been lowered by injury or other disease, but they usually suffer from a milder form.

The association of "disturbed action of the heart" (neurocirculatory asthenia) and trench fever has been noticed specially by British observers. This is probably an evidence of continued low-grade infection.

Etiology.—The causative agent is a virus of the class associated with the development of so-called Rickettsia bodies in the tissues of the insect vector of the disease. In two other "Rickettsia diseases"—*i. e.*, typhus and Rocky Mountain spotted fever—the Rickettsia bodies are present in the tissues of patients; they have also been described in the blood of patients with trench fever.

The disease has been experimentally transmitted from man to man by the injection of blood, dried urine, and occasionally the saliva from an infected patient. It is usually disseminated by the body louse which acquires the virus by biting infected individuals. After an incubation period of from seven to ten days the insects can transfer the infectious agent to man either by biting or by having their excrement or dead bodies rubbed into scratches or abrasions in the skin. The virus retains its infectivity for many months in the dried excrement of lice.

Morbid Anatomy.—As the disease is not fatal, there has been no opportunity to observe the visceral lesions. The excised cutaneous macules show a mild perivascular infiltration of lymphocytes mixed with a few polymorphonuclear leukocytes, but no endothelial necrosis. Rickettsia bodies have been described in films of blood taken from patients during the periods of fever.

Symptoms.—Period of Incubation.—The period of incubation in the louse-borne infection is usually from fourteen to thirty days.

Prodromata.—Although prodromal signs of infection are usually lacking, headache, malaise, exhaustion, insomnia, and pain in the muscles of the back and legs occasionally precede the characteristic onset.

Onset.—The onset is usually sudden and is often initiated by a chill, followed quickly by a rise of temperature to 102° or 103° F., and a proportional increase in pulse rate. There is pronounced prostration, marked anorexia, nausea which is sometimes accompanied by vomiting, marked

frontal headache, and severe pain, similar to that of myalgia, in the back and calves of the legs. Occasionally bronchial catarrh is noticeable. Frequently a characteristic rash appears early on the chest and the abdomen. All the typical signs and symptoms are usually present within twelve to twenty hours.

Course of Disease.—After the characteristic onset, trench fever may follow three different courses: there may be one short period of fever, as in influenza; the symptoms and signs may recur at five- or six-day intervals, or irregularly; or the pyrexia may persist for a long time as in typhoid or paratyphoid fever. Profuse sweating at night or at the end of a period of fever is not infrequent.

The most striking symptoms are pain and tenderness of the muscles and bones. Although the muscular pain is usually very severe, tenderness around the joints is less marked than in articular rheumatism. The frontal headache which is a common symptom is often accompanied by severe retrobulbar pain and occasionally by nystagmus, lacrimation, and conjunctivitis. The pain in the lumbar muscles and in the calves of the legs is particularly severe and acute when the temperature is highest, and, like pain in the head, is associated with a muscular tenderness which differentiates it from ordinary myalgia. The neck and shoulders are less often involved. Pain and tenderness of the abdominal muscles may at times simulate that of appendicitis or infections of the gall-bladder. In most cases pain and tenderness of the shin bones is the most distressing feature.

The typical *rash* appears first on the lower thorax and abdomen and it comes and goes usually with the fever. Although wholly absent in some cases, the rash may be quite characteristic during the relapses which sometimes occur months after the onset of the disease. The lesions consist of red macules which vary in diameter from 2 mm. to 1 cm. They may be numerous and very wide-spread or only occasional. In some cases they strongly resemble the rose-spots of typhoid fever. The macules may either disappear within a few hours or persist for several days.

As a rule, the marked *tenderness* and *enlargement of the spleen*, which develops early in most cases, fluctuates more or less. The *bronchial catarrh* so often noted during the war may have been an adventitious complication, but was sufficiently marked to be considered a definite part of the syndrome. *Anorexia*, sometimes accompanied by vomiting, is common. In over 50 per cent. of cases there is an early leukocytosis (white blood-count 12,000 or more); occasionally there is distinct leukopenia.

One of the most striking features of trench fever is its tendency to recur days, weeks, or even months or years after onset. Swift cites a case in which a relapse occurred after twenty-six months, while the writer recalls a relapse after three years. Byram and his associates state that lice have been infected by patients on the three hundredth and four hundred and forty-third day after onset.

Diagnosis.—Epidemic trench fever offers little diagnostic difficulty. Because there is no specific laboratory test for the disease, sporadic cases may be readily confused with influenza, typhoid and paratyphoid fever, dengue, myalgia, malaria, rheumatic fever, relapsing fever, and particularly with mild typhus. Diagnosis must, then, depend largely upon the recognition of the most typical features of trench fever, and upon the exclusion of the other similar diseases. The development of characteristic Rickettsia bodies

in normal body lice which have been allowed to bite a suspected patient is strong presumptive evidence of the existence of trench fever.

Prognosis.—Trench fever in itself is not fatal, but as a complication of other diseases or in association with injury it may become very serious. Most patients in fairly good physical condition are able to free themselves from the infection within a few weeks; but if soldiers are allowed to return to heavy duty too soon the disease may recur quite characteristically, though with lessened severity, even many months after the initial attack. This is also liable to occur in certain patients who are particularly susceptible to the infection. Patients probably carry the infection and may cause an outbreak of the disease wherever there are lice many months after the initial attack. This disease is of the greatest importance economically because it disqualifies for long periods large numbers of otherwise healthy persons.

Prophylaxis.—Prophylactic therapy consists of efficient delousing. As the virus present in the excreta of infected lice needs to be heated to over 70° C. to be rendered non-infectious, it is probably best to disinfest as well as to sterilize all suspected bedding and clothing at a temperature of 100° C. or more.

Treatment.—Although there is no specific treatment for trench fever, much can be done to lessen the discomfort and shorten the duration of the symptoms. Usually the pain may be mitigated or entirely relieved by such drugs as *acetosalicylic acid*, *atophan*, and *phenacetin*. Occasionally *codein* or *morphin* must be used to give relief. Electric heat, sunshine, or a hot-water bag may often provide great comfort. Physical exercise, except of the mildest possible character, should be avoided until after the fever and the resulting exhaustion have gone. During afebrile periods the diet should be as liberal as digestion will permit. The bowels must be kept freely open. There can be no doubt that rest, warmth, a liberal diet, sunlight, and fresh air are most efficient curative agents. The convalescent patient must not be allowed to return to work, even of such moderate character as that of hospital nurse or orderly, until strength has been completely recovered, because undue exertion or exposure almost always recalls the fever and pain.

HARLOW BROOKS.

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EPHEMERAL FEVER

(*Febricula*)

Definition.—Ephemeral fever denotes a febrile reaction of unknown origin which lasts for twenty-four hours and then disappears completely, pre-

senting during its course no local lesion. The same type of fever persisting for several days is termed "febricula."

The characteristic feature of these conditions is the inability to refer the fever to any specific cause or find any local lesion responsible for it. With the progress of clinical bacteriology, *x*-ray, and better recognition of hidden foci of infection, the tendency toward making the diagnosis of ephemeral fever or febricula has markedly declined.

Etiology and Symptoms.—Exposure to foul odors or to sewage gas has long been described as a cause of fever of this type. Two varieties are described. The first is an acute form with nausea, vomiting, colic, and fever. The second is subacute, consisting of low fever usually without chills. At present there is considerable doubt whether exposure to sewage gas or foul odor is the sole cause of these febrile attacks, although it has long been believed that such exposure may cause sickness.

Mild or abortive forms of the infectious diseases may produce a pyrexia lasting for one day or more without any distinctive features. The presence of an epidemic or history of contact is very helpful in determining the true cause of the fever.

Children are particularly prone to develop a fever of unknown origin which may last for a few days and then disappear. Following a change of diet or environment, such as occurs during summer vacations or camping trips, the child may abruptly complain of malaise and indisposition. The temperature will be found to be 103° to 105° F., and except for headache, loss of appetite, and malaise no other symptoms will be present. Physical examination reveals nothing but a feverish flush to the face and a dry, furred tongue. The urine is scanty, but otherwise negative. The temperature usually comes down on the morning of the second, third, or fourth day and the child then feels as well as before the attack. In such cases the lesion may be a gastro-enteritis, or an upper respiratory infection involving the tonsils, sinuses, or pharyngeal lymph-nodes. Other foci of infection, such as the teeth, genito-urinary tract, gall-bladder, or appendix, must be eliminated. When these possibilities are kept in mind the unsatisfactory diagnosis of febricula or ephemeral fever is less likely to be made.

Treatment consists of rest in bed, a laxative, and a simple soft diet. Antipyretics may be given.

HORACE S. BALDWIN.

MILK SICKNESS

(Trembles)

Definition.—Milk sickness is an acute non-febrile disease of a specific nature due to the ingestion of milk, milk products, or the flesh of cattle suffering from a disease known as "trembles."

Incidence.—At present it is rare, but in the early part of the nineteenth century the disease was common, especially along the frontiers. Isolated outbreaks are occasionally reported to occur in unsettled regions. So far as is known, milk sickness has never occurred outside the United States.

Etiology.—The specific etiology is in doubt. The work of Moseley,

Curtis, and Sackett indicates that sheep, cattle, and rabbits fed on *Eupatorium urticæ folium* (white snake root) develop trembles and may eventually die. Jordan and Harris, however, in their studies of an epidemic in New Mexico in 1907, found no white snake root in the region, and suggested as the etiological factor *Bacillus lactimorbi* which they found in the internal organs and heart's blood of animals examined a few hours after death. Moseley found white snake root to be rich in aluminum phosphate and claimed to have produced the disease by feeding this substance to rabbits and cats. Curtis in 1917 was unable to confirm this work. The limitation of trembles to certain well-defined regions and the fact that animals become affected only after exposure at night or in the morning while dew is on the grass has led McCoy to suggest that the disease might possibly be conveyed through intermediary hosts such as arthropods or insects.

Symptoms.—In man the disease is characterized by a gradual onset with weakness and loss of appetite. The vomiting, which begins after a day or two, is followed by obstinate constipation and abdominal distress. The tongue becomes large and flabby. There is no fever, although great thirst is very marked. Usually the mind remains clear, but in fatal cases coma may precede death by several hours. The average duration of the illness is about one week. The mortality is very high.

Treatment.—Prophylaxis consists in avoiding the meat and milk products of animals with trembles, and the pasturing of cattle on cleared or ploughed land. The treatment is symptomatic.

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ACUTE MONONUCLEOSIS

(Glandular Fever)

Definition.—Acute mononucleosis is an infectious and probably contagious disease characterized by a short febrile course, general enlargement of the superficial lymph-nodes, especially the cervical chain, and a mononuclear leukocytosis.

History.—In 1889 E. Pfeiffer described a disease of children, which he called "Drusenfieber," characterized by fever and enlargement and tenderness of the cervical lymph-nodes, which occurred in house epidemics. In 1896 West reported an epidemic of a similar disease in eastern Ohio. The older clinical accounts described a febrile condition lasting from nine to twenty-seven days accompanied by enlargement of the lymph-nodes, usually those of the neck, but at times those of the superficial groups as well. Occasionally the spleen and liver were enlarged. Synchronous infection of the upper respiratory tract was sometimes present. Recovery was the rule. Longcope in 1922 reported a syndrome which resembled very closely the "glandular fever" originally described by Pfeiffer, and because of the associated mononucleosis recommended that the term "infectious mononucleosis," first used by Sprunt and Evans, be employed as the appropriate name for the disease.

Etiology.—Acute infectious mononucleosis occurs chiefly in children and young adults. It is thought to be moderately contagious, but no causative agent has been isolated. The tonsils and lymphoid tissue of the upper respiratory tract are probably the paths of ingress.

Morbid Anatomy.—Almost nothing is known about the pathology of the disease. The sectioned lymph-nodes differ only from those of patients with lymphatic leukemia in the degree of hyperplasia. There were no indications of Hodgkin's disease, tuberculosis, or lymphosarcoma in Longcope's series. Studies of the oxidase reactions in one type of mononuclear cells in the blood have led to the conclusion that some of these cells are abnormal and derived from lymphoid tissue.

Symptoms.—In Longcope's 10 cases the onset was, as a rule, gradual, consisting of headache, fever, occasionally sore throat, chills, cough, abdominal pain, and sweating. The temperature varies from 100° to 103° F., and is irregular. The intermittent fever continues for two to three weeks. The patient complains chiefly of general malaise, sweats, and soreness of the pharynx, or tonsillitis.

The cervical nodes are always eventually enlarged, firm to the touch and tender; often there is general enlargement of the superficial lymph-nodes as well. The tonsils may be red, swollen, and acutely inflamed. During the course of the disease the spleen may become palpable and sometimes tender. The pulse varies from 80 to 100. With subsidence of fever, evidences of acute infection in the throat disappear and the lymph-nodes and spleen gradually return to normal size.

The unusual feature of this condition is the mononuclear leukocytosis which usually reaches its height about the tenth to the fourteenth day of the disease. With the increase in the number of mononuclear cells from 9000 to 26,000 there is an absolute reduction in the number of polynuclear granular cells to 2000 or 4000 per cubic centimeter.

Prognosis and Diagnosis.—Practically all patients recover. Diagnosis is usually easy, because of the characteristic swelling of the lymph-nodes, mononuclear leukocytosis, and short mild fever.

Treatment is symptomatic, with rest in bed.

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MILIARY FEVER

Definition.—Miliary fever is an acute infectious disease which occurs in localized epidemics, and is characterized by abrupt onset with fever, excessive sweating, prostration, and an erythematous rash with miliary vesicles and sudamina.

Incidence.—Europe and England have been subject to epidemics; and the "sweating sickness" which swept over England in five epidemics during the fifteenth and sixteenth centuries was probably miliary fever. In France an epidemic occurred in 1907. The disease has never been encountered in the United States.

Etiology.—The cause and mode of transmission of the disease are unknown. The epidemics observed have appeared more frequently in the spring and summer months. Individuals of all ages are susceptible. The mode of spread is rapid, in this respect simulating that of influenza.

Symptoms.—Sweating is the most striking feature of the disease. It begins with the onset of fever and continues throughout the course. The eruption, which appears on the third or fourth day but may be delayed, is usually of the red papulovesicular type, occurring first on the neck and back, under the breasts, in the axillæ, and between the thighs. A purpuric type occasionally occurs, with other manifestations of hemorrhage. As the rash appears there is a gradual diminution in the intensity of the symptoms followed within two or three days by desquamation. Convalescence is characterized by great weakness, anemia, and loss of weight.

Prognosis.—The prognosis is usually favorable, but fulminating cases with extreme hyperpyrexia, dyspnea, and very rapid pulse may cause delirium and death before the rash has disappeared.

Treatment is symptomatic.

HORACE S. BALDWIN.

FOOT-AND-MOUTH DISEASE

(*Epidemic Stomatitis, Aphthous Fever*)

Definition.—Foot-and-mouth disease is a highly contagious disease of cattle, sheep, pigs, and goats, which is transmissible to man. The disease is characterized by an acute febrile course and a vesicular eruption, usually located in the mucous membrane of the mouth, more rarely on the skin of the fingers, toes, or other parts of the body.

Incidence.—It is endemic in various parts of the world, and a higher incidence has been prevented only by rigid quarantine of cattle showing signs of the disease.

Etiology.—Löffler and Frosch in 1898 attributed its origin to an ultramicroscopical organism present in the exudate of the vesicles, in the saliva, and in the milk of infected animals. The transmission to man takes place, for the most part, by means of milk or butter from diseased cattle. In Germany a considerable number of cases in milk maids have been reported to follow direct inoculation of the hands in milking, and in one instance vesicles formed on the breasts as well as on the hands. Tyzzer in 1903 reported outbreaks of foot-and-mouth disease in calves inoculated with smallpox virus which had been obtained from an animal infected with foot-and-mouth disease. No cases in human beings, however, have been known to follow contamination of vaccine with the foot-and-mouth disease virus.

Symptoms.—In *cattle*, after an incubation period of two to ten days, the first symptoms are shivering, loss of appetite, stiffness of movement, and

fever. Soon profuse salivation begins and, if the mouth is examined, white vesicles can be seen on the buccal mucous membrane. Movement is impaired, and before long vesicles appear on the posterior aspect of the hoof. These symptoms last for nearly a week before they ameliorate; after two weeks all visible signs of the disease disappear.

A mild and short course characterizes the disease in *man*. Following an incubation period of two days to two weeks fever develops and often vomiting. Then on the buccal and pharyngeal mucous membranes a vesicular eruption appears which renders swallowing difficult. Occasionally this also appears on the interdigital skin of the fingers and toes. After a few days the vesicles rupture, leaving shallow ulcers which heal gradually without scars. Recovery is usual.

Prophylaxis and Treatment.—The isolation of the diseased cattle and the boiling of milk during an epidemic are important prophylactic measures. Treatment consists in the use of a mouth-wash of potassium permanganate or the application of silver nitrate or drying powders to the affected parts.

HORACE S. BALDWIN.

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PSITTACOSIS

Definition.—Psittacosis is an acute infectious disease associated with the handling of sick parrots. It is characterized by chill, fever, great weakness and depression, convulsions, and coma. The mortality is 30 to 40 per cent.

Incidence.—In France, Italy, and Germany epidemics have been described, and in 1904 Vickery of Boston reported 3 cases in the United States. A few cases have been reported in England.

Etiology.—During the epidemic in Paris, Nocard described a short, Gram-negative, actively motile, flagellated bacillus which he recovered from parrots that had died of psittacosis. Gilbert and Fournier in 1896 claimed to have recovered a similar organism from the heart blood of a woman dying of the disease.

Symptoms.—The onset is usually sudden, with a chill, high fever, and malaise. Convulsions may occur. Throughout the disease there is usually great weakness and depression. Frequently bronchitis, bronchopneumonia, or true lobar pneumonia may be present, the extent of the lung involvement determining the outcome. The disease may be mild, especially in children and young adults.

Treatment is symptomatic.

HORACE S. BALDWIN.

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TSUTSUGAMUSHI FEVER

(*Kedani Disease, Japanese River Fever*)

Tsutsugamushi fever is an acute, endemic, febrile disease limited to the island of Nippon, Japan. It is caused by the bite of the hair louse. Bacteria, protozoa, and a toxin contained in the body of the mite have, in turn, been suggested as etiological factors of the disease. The onset is acute, with a chill and severe pain in the forehead and temples. This is followed by fever and painful enlargement of certain lymph-nodes, in the region of which are one or more black or brownish necrotic areas which indicate the location of the original bite. After five to seven days a papular eruption appears on the face and soon spreads all over the body. On about the fourteenth day, with the fading of the eruption, the fever begins to remit and convalescence soon begins. The presence of the necrotic area and the absence of *Bacillus pestis* in the fluid from the infected nodes serve to distinguish tsutsugamushi fever from plague. The mortality is high, especially in patients more than fifty years of age. Quinin and salvarsan may be given.

HORACE S. BALDWIN.

AINHUM

Ainhum is a chronic disease which usually affects the fifth toe and is characterized by the formation of a furrow at the digitoplantar fold which deepens and extends until the toe is encircled and finally separated from the foot. In South America it occurs in Brazil, Argentina, and British Guiana; in Africa, the Gold Coast and the West Coast furnish most of the cases; and in the Southern United States and the West Indies the disease is also seen. Castellani and Chalmers believe that the infection is parasitic in origin and that it takes place through the small superficial lesions or wounds often found on the feet of people who wear no shoes. The disease is purely local. If left to itself, it may last for two to ten years, and eventually end in removal or sloughing of the toe. Ainhum is best treated in the early stages by longitudinal incision into the grooved furrow. In later stages amputation is necessary.

HORACE S. BALDWIN.

VERRUGAS PERUVIANA

(*Peruvian Wart*)

Verrugas peruviana is a chronic specific disease which occurs in endemics in South America, especially on the western slopes of the Andes in Ecuador, Peru, Bolivia, and the northern parts of Chile. It is characterized by fever, rheumatoid pains, anemia, and the development of granulo-

matous swellings in the skin and mucous membranes which tend to bleed. Experiments by The Harvard Commission indicate that a filtrable virus transmitted by insects is probably the *etiological factor*. The febrile stage develops after an incubation period of eight to forty days and may last from twenty days to eight months. As the nodular eruption develops on the mucous membranes and skin of the face, neck, and extensor surfaces of the arms and legs, the fever declines. The stage of eruption is distinguished from frambesia by the absence of the nodules on the trunk, by the tendency to hemorrhage, and the absence of *Treponema pertenue*. The mortality varies from 10 to 40 per cent. No *specific treatment* is known. Administration of arsenic subcutaneously and the sending of the patient to the coast are said to be efficacious.

HORACE S. BALDWIN.

GANGOSA

(Granuloma Gangrenosum)

Gangosa is a chronic disease of the tropics, characterized by ulceration of the palate, nose, pharynx, and skin, with ultimate destruction of cartilage and bone, particularly that of the nose and larynx. Several authors believe it to be a sequela of yaws. No causative agent has been found. The disease may begin as a sore throat. A short time later a nodule develops on the back of the pharynx, the posterior pillars of the fauces, or the edge of the soft palate. This ulcerates until gradually, as the soft parts slough away, the bone of the palate, the nasal septum, and the cartilages of the nose are eroded. In some advanced cases the entire front of the face becomes a large opening ringed about by foul-smelling ulcers. Occasionally the lesions appear on the skin of the extremities or on parts of the body not usually covered with clothing. Patients always tend to recover, but very slowly. The permanent disfigurement is great. The best therapeutic results are obtained with salvarsan.

HORACE S. BALDWIN.

RAT-BITE FEVER

Definition.—Rat-bite fever is an acute infectious disease contracted from the bite of a rat, and characterized by relapsing fever and an exanthematous rash.

Incidence.—The disease has long been recognized in Japan, and for many years reports of sporadic cases have appeared in American medical literature. Horder reported 3 cases from England in 1909, and since that time an increasing number of cases have been seen there. A few have also been reported in France, Spain, Italy, and Germany.

Etiology.—The identity of the specific etiological agent of rat-bite fever has not been definitely ascertained. Ogata was the first to transmit the disease to guinea-pigs by causing rats to bite them. Other Japanese have confirmed his work and have isolated spirochetes which are short, round, highly motile, and stain easily. Schottmüller, Blake, and Tileston obtained streptothrix in smears or in cultures from the blood of patients with rat-bite fever.

Symptoms.—After the bite of an infected rat, or of other animals such as the ferret, weasel, or cat which have come in contact with infected rats, there is an incubation period which varies from a few days to several months. The original wound at first heals uneventfully; later it becomes red, edematous, and tender. Lymphangitis and adenitis follow. Suddenly the patient has a chill, becomes feverish, acutely ill, markedly prostrated, and sometimes delirious. With the onset of the fever there appears a cutaneous rash of the exanthem type, consisting of bluish-red, edematous, sharply marginated macules which may measure as much as 10 cm. in diameter. After a few days the temperature falls by crisis and the symptoms subside. Several days then pass before a relapse occurs similar to the previous attack, but usually less severe. These relapses may occur for several months, each becoming less severe.

According to Blake, the more important *complications* are nephritis, severe anemia, and emaciation. Some patients have an abortive type of the fever with no relapses and an early recovery. The mortality is 10 per cent.

Treatment.—Immediate cauterization of the bite with phenol or the actual cautery has been advocated by Miyake as an efficient prophylactic measure. Hata introduced salvarsan therapy for this disease in 1912 and other observers have since reported that it gives favorable results.

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TULAREMIA

(Deer-fly Fever; Rabbit Fever)

Tularemia is an acute infectious disease caused by the *Bacterium tularense*. It is primarily an infection of rodents, especially rabbits, but occurs occasionally in man as an accidental infection.

History.—McCoy, in 1911, described "a plague-like disease of rodents," prevalent among the California ground squirrels. McCoy and Chapin, in 1912, discovered the causative organism of the disease and named it *Bacterium tularense*. Francis isolated this organism from 7 human cases and 17 jack rabbits in 1920, and named the disease "tularemia." Mayne and Francis proved the deer-fly, *Chrysops discalis*, to be a transmitter of the infection in laboratory animals.

Incidence.—Up to the present time tularemia has been observed only in the United States. Authentic reports of cases have been made from thirteen states, extending from the Atlantic to the Pacific coast; 3 cases of *B. tularense* infection of the eye have been reported.

Etiology.—Tularemia is caused by a micro-organism known as *B. tularense*. This may be obtained from the blood of patients suffering from the disease, or by cultures from the blood, spleen, or liver of animals dying of the disease. Cultures should be taken on coagulated egg-yolk or serum-glucose-cystin-agar, in which the organism grows as a small, non-motile, Gram-negative rod. The organism will not grow on plain agar.

Altogether 49 cases of this disease have been observed in man; 14 of these were caused by fly-bite, and 1 by tick-bite; 20 of the patients apparently contracted the disease from handling rabbits, and 14 were laboratory workers who had performed autopsies on infected guinea-pigs or rabbits while studying the disease. Apparently the danger comes not from handling live rabbits, but from the dressing of dead rabbits for food.

Pathology.—Animals infected spontaneously or experimentally with this disease show enlargement, and in some cases caseation, of the lymph-glands, and great numbers of small white foci of necrosis studded over the spleen and liver.

Comparatively little is known of the morbid anatomy of tularemia in man, as patients rarely die of the infection. There is local induration, redness, and pus formation at the original point of infection, with swelling of the regional lymph-glands; occasionally an abscess is formed in the enlarged lymph-nodes.

Pathogenesis.—Infection takes place through the skin. In cases caused by fly-bite or tick-bite a papule develops at the point of infection, and speedily breaks down, leaving an ulcer about 0.25 inch in diameter, with raised edges and a punched-out appearance. Strangely enough, laboratory infections are characterized by absence of any focal lesion. Hence the portal of entry of infection in such cases is unknown; presumably, however, infected tissue and blood find lodgment on the patient's hands; then the bacteria either penetrate the skin or find their way to the mouth and are swallowed.

Insect Transmission.—The only animals found infected in nature are the ground squirrels and wild rabbits. These rodents, which constitute the great reservoir of infection, die of bacteremia, thus affording the necessary conditions for transmission by blood-sucking insects. Transmission from rabbit to rabbit is effected by the rabbit tick and the rabbit louse, neither of which bite man. Transmission to man is by the deer fly (*Chrysops discalis*) and the wood tick. The *Chrysops discalis* is commonly found on horses in certain Western states. The wood tick, *Dermacentor andersoni*, is common in Montana and adjoining states.

Under laboratory conditions transmission has been effected among white mice by the mouse louse and the common bedbug; from guinea-pig to guinea-pig by the stable fly; and from ground squirrel to ground squirrel by the squirrel flea.

Symptoms.—Two clinical types of this disease have been described: the glandular type and the typhoid type.

1. *Glandular Type.*—The incubation period varies from two to five days or longer. The onset is sudden, often occurring while the patient is at work. It is manifested by headache, fever, chills, muscular pains, vomit-

ing, and prostration. Within forty-eight hours after onset there is pain in the area of the lymph-glands which drain the site of infection. On examination the glands are found to be enlarged and tender. A few hours later the site of infection becomes swollen and painful, and a papule forms at this point which rapidly breaks down with the formation of a small ulcer. The latter has a raised, punched-out margin. Fever lasts from two to three weeks, and may reach 104° F. There may be daily remissions to almost normal temperature, suggesting a septic process. In about half the cases the lymph-glands nearest the point of infection proceed to suppuration, and the abscess may rupture through the skin at this point. The blood-count shows very little of interest, although the leukocytes are increased in some cases. During the second week of the disease agglutinins for *B. tularense* appear in the blood.

Convalescence is slow, usually several months in duration. Patients finally recover without evident complications. Death is rare. Francis reports one case in which the patient died from complicating pneumonia. One of Anderson's patients suffered from an associated heart lesion, and died during the fourth week of his illness. In another of the reported cases the patient died following an exploratory abdominal operation.

2. *Typhoid Type.*—This type occurs in laboratory workers who have performed autopsies on infected guinea-pigs or rabbits. In these patients there is no evident site of infection or enlargement of the lymph-glands, but in all other respects the symptoms are the same as those of the glandular type.

Diagnosis.—Acute febrile symptoms in a person who has dressed or cut up wild rabbits should suggest tularemia, particularly when the fever is accompanied by local infection on the hand, and swelling of the cervical, epitrochlear, or axillary lymph-nodes. Diagnosis of tularemia is readily made by agglutination tests with the patient's serum. Reactions are negative with *B. typhosus* and positive with *B. tularense* in high dilutions.

The diseases most likely to be confused with tularemia are typhoid fever, anthrax, and septic infection. The final distinction can be made only by the isolation of the organism or by agglutination tests.

Treatment.—The treatment is symptomatic. Surgical intervention is not advisable until the glands are on the point of breaking through the skin. No preventive vaccine or curative serum has been perfected.

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THE MYCOSES

ACTINOMYCOSIS

Definition.—Actinomycosis is a chronic infection caused by the *Actinomyces bovis*, or ray fungus, and is characterized by the formation of abundant granulation or connective tissue, and by multiple abscesses which discharge an exudate containing colonies of characteristic yellowish granules.

History.—In 1877 Bollinger demonstrated that the disease of cattle commonly known as "lumpy jaw," and regarded as a form of sarcoma, was due to a vegetable parasite named by Harz "actinomyces bovis" because of its radiate structure. In 1878 J. Israel found the parasite in man, and in 1879 Ponfick pointed out the identity of the human and bovine infection. Wolf and Israel made the first extensive study of the biology of the organism.

Incidence.—The disease is widely distributed, and more common than is generally supposed. Sanford has recently made an interesting study of the distribution of actinomycosis in the United States, and collected 678 cases, representing practically every state in the Union. The disease was shown to be especially prevalent in the upper Mississippi Valley and the northwest portion of the country; 157 cases were observed at the Mayo Clinic between 1913 and 1922. Sixty-three cases were observed at the Massachusetts General Hospital during a period of twenty years. Males are much more frequently affected than females. The disease is most common in early adult life, between the ages of twenty and forty years, although it may occur at any age. Occupation is not so important as was formerly believed.

Etiology.—Infection may take place through implantation of the parasite within the tissue by a foreign body, such as grain beards and splinters. The failure of true *Actinomyces bovis* to grow at other than body temperature and the prevailing location of the disease around the jaws and neck suggest that infection takes place from the mouth, from which it may be transmitted to other parts of the body by way of the respiratory and alimentary tracts. Whether the organism is normally present in the mouth, and invades the tissues whenever trauma makes this possible, or whether it is ingested with the food is still a moot question. That organisms in the buccal cavity are the cause of the disease is further suggested by the development in guinea-pigs, following intraperitoneal inoculation of the contents of carious teeth and tonsillar crypts, of omental tumors histologically iden-

tical with actinomycotic tissue, and containing typical club-bearing actinomyces granules. There is little evidence that the disease is contagious, and direct infection from cattle is improbable. However, Cope and McWilliams each report a case in which the disease developed at the site of a bite.

Bacteriology.—The micro-organism occurs in pus and tissue as rounded or spherical granules, which vary in size from very minute particles to forms about 1 mm. in diameter. They are usually yellowish (hence the term "sulphur granule"), but may be red, gray, or dirty white. An aggregation of them at times produces a mulberry-shaped mass. The granules consist of a central mass of tangled filaments, débris, and pus cells, a paracentral zone of interlacing filaments, and at the periphery radially disposed club-shaped hyaline and refractive bodies with central filaments. When crushed they are found to contain slender Gram-staining, branched, and unbranched wavy threads. The true clubs are stained by eosin. Owing to the overgrowth of contaminating bacteria pure cultures are obtained with difficulty. *Actinomyces bovis* is a facultative anaërobe. In glucose-agar, growth is most abundant in a narrow zone 5 to 10 mm. below the surface. In bouillon cultures, whitish coherent spherical masses develop at the bottom of the tubes, but there is no clouding of the media. Intraperitoneal inoculation of animals produces connective-tissue nodules which contain cavities filled with pus and typical club-bearing actinomyces granules.

Morbid Anatomy.—Multiple small recurrent abscesses, communicating channels, and discharging sinuses containing the parasite occur, and are usually surrounded by a wide zone of granulation or connective tissue due to proliferation. Diffuse inflammation is uncommon, but at times large encapsulated abscesses develop. The lesion may be a small nodule beneath the skin or mucous membrane, or a fixed, diffuse, hard mass, 12.5 to 15 cm. in diameter. The process may be slow and indolent, and take months or years to develop, or it may be rapidly fulminating. An indurated mass which later breaks down is most common. Metastasis through the blood-stream is rare; the infection commonly spreads by continuity. Secondary lesions are of the indolent type, densely indurated, and may heal. Mixed infection is common. Microscopical examination shows granulation tissue and proliferation of connective tissue. Giant-cells are not uncommon. The granules are surrounded by a zone of pus-cells.

Any tissue or organ of the body may be attacked. Actinomycosis of the head and neck is most common, and occurs in more than 50 per cent. of the reported cases. The abdomen is infected in from 20 to 30 per cent., and the thoracic cavity in approximately 15 per cent.

Symptoms.—The disease usually runs a chronic course. The clinical manifestations vary. Usually there is stiffness, with associated pain and swelling in the region affected.

1. In the *cervicofacial type* the submaxillary region is most often the primary site, and the disease spreads to the neck by extension. The jaw may begin to tighten, and in some cases trismus with painful, tender swelling about the teeth develops. Flat, hard, circumscribed or diffuse tumor-like swellings form. Pain may be severe and throbbing, or entirely absent until the mass breaks down. The skin is normal or dusky red. The mass is usually brawny without true fluctuation, but its surface may be uneven because of small areas of softening which produce a doughy feeling on pal-

pation. In some cases there is a collection of tumors with smooth, regular surface, and dense, uniform consistency. Multiple discharging sinuses and fistulæ eventually form. The cheeks, the region of the masseter muscles, and the parotid may be invaded, or extension to the skull, meninges, and brain may take place. If the base of the tongue or anterior cervical region is affected, dysphagia is occasionally an early symptom; and if the process attacks the hypopharynx or epiglottis, dyspnea results. In the cervical region the abscesses are commonly elongated, superficial, and multiple; the skin over them is folded in linear striations.

2. In the *abdominal type* there may be anorexia, pain, nausea and vomiting, diarrhea or constipation, fever of an irregular type, pallor, chills, sweats, and emaciation. The condition may not be recognized until the tumor-like masses of uneven contour develop. As the disease progresses the lesions extend to the abdominal wall and sinuses and fistulæ form. Any abdominal organ may be affected.

The disease may invade the thorax, erode the vertebræ, involve the spinal cord, or extend into the pelvis, where discharging sinuses develop in the perineum.

3. The *pulmonary form* is manifested by coughing, expectoration, increasing dyspnea, slight fever, loss of weight and strength, night-sweats, pallor, and emaciation. The sputum contains blood in about half the cases, and fatal hemoptysis sometimes occurs. Pleural pain is common. The signs are those of bronchitis, pulmonary infiltration, or cavity formation. The disease is usually unilateral and basal. There may be dry pleurisy or encysted pleural fluid. Perforation of the chest wall is more common in this disease than in any other, and occurs in over 80 per cent. of the cases. The infection becomes generalized only in rare instances, and produces a syndrome resembling pyemia.

Diagnosis.—The diagnosis must be based on the clinical syndrome, the finding of the sulphur granule in the exudate or lesions, and the demonstration microscopically of actinomyces. Only typical granules with true clubs can be considered pathognomonic. If the disease is in the tongue, or if there is a great deal of secondary infection, microscopical examination of a specimen of tissue is essential to corroborate the clinical evidence. The disease may simulate tuberculosis, tuberculous adenitis, syphilis, malignancy, sinuses from dental or tonsillar infections, and various suppurative lesions. Indolent inflammatory processes with dense induration and multiple abscesses, sinuses, and fistulæ are suggestive of actinomycosis, especially when they occur about the buccal cavity or neck.

Prognosis.—The most important single factor is early diagnosis; patients treated early almost invariably do well. The outlook varies with the location and extent of the lesions. The disease usually lasts for months or years. The cervicofacial type runs a relatively favorable course, with recovery in 75 per cent. or more of the cases. Relapses may occur. In advanced cases, with extensive involvement of the head, intracranial extension may develop; or in cases of extensive supraclavicular or cervical masses, the chest may become involved in spite of treatment. Patients with the abdominal form have a less favorable prognosis; only one-third to two-thirds recover. The pulmonary type is most serious; death usually occurs within six months or one year. However, recovery has followed surgical intervention in a number of instances.

Treatment.—Care of apical abscesses, pyorrhea, and other dental and stomatic infections are important prophylactic measures. Punctured wounds and implanted foreign bodies should receive prompt and adequate attention.

Measures other than surgical are of uncertain value. Carious teeth should be removed. Small, easily accessible lesions may be successfully excised. When more extensive and less favorably placed, abscesses, sinuses, and fistulæ may be incised, curetted, and drained. Repeated operations may be necessary. In the abdominal type of the disease, extirpation of the lesion is advisable when it is accessible and circumscribed. More conservative surgery is applicable to diffuse types. In pulmonary actinomycosis incision, curetting, and cauterization have been curative. Early operation is important. Supplementary treatment with iodids is often helpful. Exposure to *x*-rays and radium has been recommended, but is of doubtful value.

STREPTOTHRICOSIS

Much difference of opinion prevails regarding the Streptothrix group (Streptothrix asteroides, atypical actinomyces, Cladothrix, and Nocardia). The term "streptothrix" is justified by common usage. The wide distribution of these organisms outside the body and the biology of the pathogenic varieties suggest that infection takes place from the outside world. In fresh material the organisms are found as isolated or interlacing, slender, branching, Gram-staining filaments. Their arrangement in loose clusters contrasts with the compact aggregations of actinomyces granules. A resistance to decolorization by acids and alcohol after staining with carbolfuchsin is characteristic of certain members of the group. True club formation is absent, but club-shaped swelling of the terminal portion of filaments may be observed. Growth takes place under aërobic conditions on all culture-media at room and incubator temperature. In bouillon, ball-like masses form at the bottom of the tube, but there is no clouding of the medium. Animal inoculation may be negative or produce local abscesses. After intravenous inoculation there may be widely disseminated yellowish, miliary, tubercle-like nodules.

The *lesions in man* are suppurative and resemble those of actinomycosis, with the formation of abscesses and granulation tissue. The lung is the usual site of trouble and may show evidences of bronchopneumonia, multiple abscesses, gangrene, bronchiectasis, and induration. Empyema and perforation of the chest may occur. Metastasis may cause cerebral, subcutaneous, or other abscesses to develop. The infection is either acute or chronic. The *clinical manifestations* may closely resemble those of pulmonary tuberculosis or pyemia. Unlike actinomycosis, the streptothrix is not prone to cause lesions about the head and neck. All patients with pulmonary streptothricosis, diagnosed satisfactorily by demonstration of the organism, have died. Schottmüller and Fränkel's patient, with repeatedly positive blood-cultures, recovered.

No *specific treatment* is known. Abscesses should be treated by the usual surgical measures.

SPOROTRICHOSIS

Sporotrichosis is a chronic infection, usually confined to the skin and underlying tissues, and is characterized by the formation of gumma-like

nodules, abscesses, and ulcers. It is due to a filamentous spore-bearing fungus of the genus *Sporotrichium*.

Occurrence.—The first case was reported by Schenck. Meyer in 1916 collected 82 cases, 50 of which were diagnosed by culture; and a number have since been reported. The disease is widely distributed and is more frequent among males and in the country districts. Most cases reported in the United States have been in the Middle West. The parasite may develop as a saprophyte on vegetable matter. Sporotrichosis occurs in horses, dogs, and rats. There is a history of abrasions, or incised or penetrating wounds in some cases. Infection may be transmitted from person to person and by the bite of animals. Insects and animals may act as passive carriers. Meyer infected himself while working with an equine strain.

Etiology.—The fungus can rarely be demonstrated in pus or in tissue by direct examination, but may be found after long search as elongated or oval bodies of irregular shape and size (2–10 x 1–3 micra), frequently pointed at one end, often budding, usually single, at times radially arranged about a central spore. A large amount of material must be used for the inoculation of cultures. Growth is aërobic and occurs on all culture-media at room and incubator temperature. A week or more may elapse before the first colonies appear. Separation into two species, *Sporotrichium schencki* and *Sporotrichium beurmanni*, is probably not justified. Cultures show a Gram-staining, branching, septate mycelium and spores, which stand a temperature of zero to 55° C. Page, Frothingham, and Page obtained growth from a dry culture two years' old. Rats inoculated with the culture develop septicemia without nodules or multiple lesions in the internal organs. After intraperitoneal inoculation of male rats peritoneal lesions develop and the testicle becomes infected.

Morbid Anatomy.—The gumma-like nodules usually consist of a central abscess surrounded by granulation tissue with giant- and epithelioid cells and a peripheral zone of connective tissue, histologically resembling syphilitic, tuberculous, or other chronic inflammations.

Symptoms.—The *incubation period* is variable, such extremes as twenty days and three months being recorded. The chance discovery of a "gumma" may be the first intimation of the disease. This appears as a hard spheric, elastic, movable, subcutaneous nodule, not adherent to the overlying skin, gradually increasing in size to a diameter of 20 or 30 mm., and remaining unattached below, but finally becoming adherent to the skin which becomes pink to purplish in color. After four to six weeks a cold abscess is formed with fluctuation in a central area surrounded by a resistant zone of induration. Further development may cease or an open or crust-covered ulcer form with irregular, indurated, undermined, violet tinged, or at times brownish-red margins, under which pus may collect. The ulceration may last months or years. Cicatrization may occur. The lesions are usually painless. The general health may be undisturbed, but slight fever is common.

The disease may remain *localized*, usually in the upper extremity. Cord-like indurated lymphatics extend from an initial "chancre," and along their course gummata, abscesses, and ulcers develop. The regional lymph-glands are usually not involved. In the *disseminated gummatous* form, single or successive crops of nodules develop at intervals. In rare instances there is an acute onset with fever, a rapid development of multiple

lesions due to *general dissemination*, and the syndrome of septicemia. Extracutaneous lesions may appear in various parts of the body.

Diagnosis.—The disease may simulate syphilis, tuberculosis, blastomycosis, glanders, leprosy, or pyogenic infection. It may be distinguished from these diseases by cultivation of the sporothrix. Early diagnosis is important for successful treatment. The *complement-fixation test* with the sporotrix as antigen is probably not specific. *Intradermal injection of a suspension of sterilized spores* gives positive reactions, which, however, may occur in other than sporothrix infections.

Prognosis.—Uncomplicated sporotricosis is rarely fatal. When untreated it persists for months or years, but appropriate treatment is usually followed by rapid arrest.

Treatment.—Iodid of potash should be given in slowly increasing doses (up to 4 to 6 gm. or more daily). If not well tolerated by mouth, it may be administered by rectum. Treatment should be continued for at least a month after apparent recovery. If absorption of closed abscesses is slow, they may be punctured, aspirated, and injected with a weak solution of iodid. Incision and curettage are to be avoided. Ulcerated lesions may be painted with tincture of iodin and dressed with a solution containing water 500 c.c., potassium iodid 10 gm., and iodin 1 gm.

BLASTOMYCOSIS

Blastomycosis is a granulomatous and suppurative process in which multiple abscesses form in the skin and subcutaneous tissue and sometimes in the lungs and other internal organs. Over 140 cases of cutaneous infection and over 40 cases of systemic involvement have been reported.

Incidence.—Most of the cases cited in America have been observed in and about Chicago, but the disease is quite generally distributed throughout the United States, Canada, Porto Rico, and many foreign countries. Males are more frequently affected than females. The method of contagion has not been established. Abrasions may be a portal of entry.

Etiology.—*Blastomycetes* are found in the lesions, pus, and sputum, and appear as Gram-staining, oval, or spheric bodies (7–10 micra), with a double contoured hyaline capsule and finely granular protoplasm. Multiplication takes place in the lesions by budding. Growth occurs at room and incubator temperature, and on solid media is yeast-like. Mycelia and aërial hyphæ form. Inoculated animals inconstantly develop abscesses surrounded by granulation and connective tissue. Male guinea-pigs usually develop testicular lesions after intraperitoneal inoculation.

Morbid Anatomy.—The typical skin lesions are elevated patches, with a rough, uneven, and scaling or papillomatous surface, and irregular, abrupt, sloping dark red margins. Miliary abscesses may be seen at the border of the patch. The skin may also show multiple nodules the size of a pea or larger; crusted or open ulcers; fistulæ or scars. When the lungs are involved there are miliary to pea-sized abscesses, or confluent areas of softening. Microscopical examination shows a central area of necrosis containing *blastomyces*, about which there is granulation tissue with multinuclear giant-cells. Other organs may be similarly affected.

Symptoms.—The disease is usually chronic with exacerbations and remissions over a period of years. Infection may be limited to the skin. In rare instances the initial symptoms are pulmonary. Pulmonary and

systemic invasion may be simultaneous. In the *pulmonary form* there is coughing and expectoration of mucopurulent and at times blood-stained sputum. Physical examination reveals signs of consolidation over the involved regions. In the *systemic form* the clinical features are those of pyemia. *Blastomyces* have been found in skin lesions, abscesses, sputum, spinal fluid, urine, feces, and blood.

The cutaneous lesions may be confused with those of tuberculosis, carcinoma, mycosis fungoides, and syphilis. The pulmonary infection is likely to be confused with tuberculosis. Systemic infection may be mistaken for glanders. The cutaneous form lasts for years. Of Montgomery's 32 patients, only 2 died from the disease. The systemic form is dangerous. Of 29 patients seen by Stober, only 3 recovered.

Treatment consists in improvement of the general nutrition and the administration of potassium iodid, of which as much as $\frac{1}{2}$ ounce or more may be given daily. Local lesions may be excised, aspirated, drained, irrigated with 1 per cent. copper sulphate solution or iodin, or exposed to *x*-rays.

COCCIDIOIDAL GRANULOMA

Coccidioidal granuloma is an infection caused by a mold which produces lesions like those due to blastomycosis. Wernicke and Pasadas, in Buenos Ayres, reported the first case. Dickson has reviewed the literature, and reported a series of cases. Over 50 have been recorded, the majority from California. The micro-organism, *Coccidioides immitis*, closely resembles blastomyces, but its growth in tissues differs in that there is absence of true budding, while multiplication takes place by endosporulation. It is more pathogenic for animals. The outlook is unfavorable, although 2 patients are known to have recovered.

SACCHAROMYCOSIS

(*Oïdiomycosis*)

Saccharomyces (or yeast) differs from the *Coccidioides immitis* in the usual absence of mycelia. Reproduction is accomplished by budding. Human infection appears to be rare. Busse and Curtis have each reported a fatal case.

TORULA

Torula is distinguished from other yeast-like organisms by the absence of endospores and of mycelia, reproduction taking place both in tissues and in cultures by budding. Stoddard and Cutler have presented suggestive evidence of torula infection in man, and Sheppe has collected reports of 11 cases, including one of his own, in which the infection was pulmonary. The organism has an apparent elective affinity for the nervous system. The cerebral symptoms resemble those of meningitis or brain tumor. The spinal fluid contains more polynuclear leukocytes and lymphocytes than normal. The organisms may be found in the spinal fluid. The outlook is unfavorable. One patient with bone and muscle involvement recovered.

MYCETOMA

(*Madura Foot*)

Mycetoma is a chronic infection affecting principally the foot, in rare instances the hands and other parts of the body. It is characterized by

multiple abscesses and sinuses, and the development of granulation and connective tissue. The lesions invade the soft parts and bone, without metastasis or invasion of the internal organs. The specific cause is contained in the white or yellow "ocroid," or deep brown or black "melanoid" granules which appear in the discharges from the affected region. The cultural characters of organisms obtained from the granules vary and must be studied further. Carter first established the specific nature of the disease. Musgrave and Clegg have discussed its etiology; and Boyd and Crutchfield have reported 30 cases observed in North America. The disease is endemic in certain parts of India.

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SPRUE

(*Psilosis, Indische Spruw, Cochin-China Diarrhea, Chronic Endemic Enteritis of Hot Countries, Intestinal Moniliasis*)

Definition.—Sprue is a chronic wasting disease of tropical countries characterized by a sore and excoriated tongue, excessive intestinal fermentation, and light colored and frothy stools. It is believed by the writer to be due to colonization in the digestive tract of a fungus, *Monilia psilosis*, which generally takes place during a preliminary digestive insufficiency, which, in turn, is frequently the result of an ill-balanced diet.

History.—Sprue was first identified as a distinct disease of the digestive tract in 1766 by William Hillary, an English practitioner in Barbadoes. Very little more was heard of this affection until about a century later, when the French described it under the name of Cochin-China diarrhea, but confused it with dysentery. In 1880 Manson and (at the same time) van der Burgh struck the die by which we shall ever recognize tropical sprue as a clinical entity. In 1901 Kohlbrügge ascribed the disease to an Oïdium infection. In 1913 Bahr, in Ceylon, considered it probable that it was caused by *Monilia albicans*. In 1914 Ashford described *Monilia psilosis* as the cause of sprue, but as yet the etiological rôle of this organism has not been universally accepted, although much corroborative evidence is accumulating which shows that the disease is a moniliasis of the digestive tract. Other prevalent theories as to the causation of sprue are that it is a deficiency disease, and that it is merely a state or condition brought about by physiological glandular insufficiency.

Incidence.—The best-known focus of sprue lies in the Malayan Archipelago, extending north to China, south to Australia, east to Korea and the Philippines, and west to India, including practically all of the intermediate islands, and confining itself largely to tropical regions. In the New World sprue is frequent in the West Indies and has probably extended to the Southern States of the Union (Wood). No cases were found in Brazil by Ashford during an extended visit to that country and no cases have been reported there.

Etiology.—The preliminary condition is usually an exhaustion of the digestive glandular apparatus, with a marked diminution in the ferments which break up the carbohydrate and fat molecules. These substances fall a prey to banal intestinal flora which produce an excessive quantity of gas and an increase in the acidity of the intestinal contents. In this sweet, acid medium the fungus *Monilia psilosis*, which usually passes through a normal digestive tube like so much waste (Anderson), finds ideal conditions for colonization, and produces the clinical picture we know as sprue.

Sprue is particularly apt to attack members of northern races who visit or settle in endemic foci, and who find the freshly killed meats, the creamless milk, and the unfamiliar and often mawkish vegetables of the tropics distasteful. Such individuals unconsciously increase the quantity of the carbohydrates and fats ingested, eat canned foods, and probably greatly weaken or even exhaust their diastase and lipase production. The native-born population of white and mestizo blood are notoriously intemperate in their habits of eating cereals, sweets, and greasy foods, and furnish absolutely, although not relatively, the larger number of cases. Sprue is rare in the full-blooded negro.

It can thus be understood why sprue is largely an urban disease in countries where fresh vegetables are abundant only in the rural districts, and where poverty prevents excessive ingestion of cereals and fats. In fact, sprue is pre-eminently a disease of the intellectuals and the well-to-do in the tropical centers affected. Such people who are able to choose their food seem to crave carbohydrates and fats. That neither climate nor an unbalanced diet are alone responsible for sprue is seen in the apparent absence of the disease from the Canal Zone, from Brazil, and from certain other tropical regions.

Sprue is probably communicable only when the intestinal canal of the recipient offers a favorable medium for the growth of *Monilia psilosis*, but the sudden appearance of sprue in persons who make a short visit to endemic foci, before there is time for exhaustion of the digestive apparatus, seems to indicate that it is possible to acquire the disease by infection alone.

Mycology.—*Monilia psilosis* is a yeast-budding fungus with a large,

predominantly round, refractile yeast form and mycelium which develops exuberantly as the medium becomes less favorable to the organism. It regularly ferments glucose, levulose, and maltose bouillons with the formation of acid and gas, and about one-third of the time ferments saccharose and galactose. It fails to ferment the other sugars and, except in the case of mannite and dextrin, reduces the acidity of their medium. It alkalinizes but never acidulates or clots milk. It fails to liquefy gelatin. Stab-cultures produce a growth resembling an inverted pine tree. Old giant cultures are brown, and have a verminous-like center with a smooth, soft, well-outlined border on Sabouraud glucose agar.

It is at times difficult to distinguish *Monilia psilosis* by morphology and culture from certain varieties of *Monilia* or *Oïdium albicans*, a much confused and very inconsistent species which may turn out to be a group of related species. In such case the definite distinction can be seen in that *M. albicans* produces a thick, tough, white membrane on a susceptible mucous surface, whereas *M. psilosis* never produces a membrane, but, on the contrary, a raw surface.

Morbid Anatomy and Physiology.—Observers in general agree upon the pathological findings in sprue. These are infiltration of the mucosa and submucosa by embryonic cells of the vessel-bearing connective tissue, strangulation of glandular ducts, destruction of the epithelial layer, and eventual thinning of the intestinal wall, and are all indications of a true atrophic inflammation of the gland-bearing mucous membrane. Minute ulcers of the whole intestinal wall are reported by some as characteristic. The wasting of liver, pancreas, and other glands of this type seems simply part of the inanition which accompanies sprue. Yeast cells and mycelial threads have been found invading the mucous membrane of tongue, esophagus, and small intestine.

Symptoms.—Bearing in mind that sprue usually develops after the appearance of a symptom-complex produced by an ill-balanced diet, this group of symptoms must be separated from those of the syndrome which, when fully developed, is so readily and universally recognized as tropical sprue. This was done when Ashford's series of 227 cases, presenting only the syndrome of dietary unbalance and negative for *Monilia psilosis*, were compared with 633 cases of true sprue in which *Monilia psilosis* was present. The prevalent lack of balanced diet in Porto Rico, believed to be a fair example of that of the American tropics, produces a capricious appetite, acid gastric dyspepsia, excess of intestinal gas, constipation, either alone or alternating with "loose bowels," a reduction in the size of the liver, and a diminution in the normal intestinal ferments. These symptoms are generally accompanied by nervous instability, psychic depression, forgetfulness, mental hebetude, asthenia, insomnia, vague body pains, palpitation of the heart, coldness and numbness of the limbs, low temperature and blood-pressure, sallowness, muscular cramps in lower extremities; moderate loss in weight, and faint brown pigmented areas, especially over forehead, malar prominences, and forearms. Such a state, however, even when the saliva becomes acid and the tongue shows mild irritation, should not alone justify a diagnosis of sprue. A similar picture may be seen anywhere, although in the tropics it may mark the onset of sprue and always demands a serologic test for moniliasis and cultures for *Monilia psilosis*.

When, however, this syndrome is greatly enhanced, and a partially or

entirely raw tongue, a white, frothy diarrhea, rapid and extreme loss of weight, and anemia occur, the diagnosis of sprue on clinical grounds is justifiable. It is of interest to note in this connection that of 976 of Ashford's cases in 1921 and 1922 not clinically diagnosed as sprue, only 1.2 per cent. were found to be carriers of moniliasis, while 85.5 per cent. of the 740 clinical diagnoses of sprue were confirmed by serological and mycological examination.

In sprue the patient is no longer ailing, but sick. The history of a *typical case* is that of a series of exacerbations, often improperly termed "relapses." The stools become very bulky, foamy, white or light grayish yellow, and of a fetid, yeasty, pungent, or "sour honey" odor. Defecation is not very frequent, but is extremely exhausting, although it gives relief because of the expulsion of gas. Abdominal pain is not common, and tenesmus with blood and mucus is not characteristic.

The *tongue* may not be involved at first, but one day the patient becomes aware that it is sensitive to seasoned foods. Partial or complete excoriation usually follows. Preceded by minute vesicles, the rawness is especially prominent in the anterior third of the tongue, where the papillæ stand out as swollen red points. Subsequent to this excoriation it is not unusual for a general stomatitis to develop, involving even the lips, buccal mucous membrane, and palate. These symptoms, when associated with burning of the esophagus and stomach and soreness of the rectum, justify the patient's complaint that he is "raw from mouth to anus." Amelioration of this extreme rawness of the tongue is frequently heralded by an exacerbation of the classical white or yellow, frothy diarrhea, with its excess of fat, high acidity, and reduction in intestinal ferments.

The remainder of the syndrome is an exaggeration of the *deficiency*. There is loss of hemoglobin, and, to a lesser degree, of erythrocytes, a relative lymphocytosis, and a tremendous reduction in weight with extreme asthenia. There is an increase in the quantity of non-protein nitrogen in the blood, with reduction of the amount of uric acid, urea, and chlorids in the urine. The pallor brings out the Addisonian-like pigmentation very strikingly. The mind is unaffected.

The Cachexia of Sprue.—Sprue is a disease that veritably dissects its victim. The patients either are bedridden or crawl about like living skeletons with an uncanny insistence on still "getting about." All of the symptoms mentioned above become more accentuated. The tongue, which becomes small, pointed, somewhat immobilized, usually free from papillæ, smooth and glistening, looks and feels like a piece of cartilage, but from one day to another may become like a piece of raw beef, and thus not only render eating difficult, but even talking or swallowing. The diarrhea is fairly constant at this stage and is lienteric, at intervals almost choleriform. The anemia increases and the blood-picture is apt to resemble that of pernicious anemia. Death occurs from inanition and exhaustion.

Complications.—Weakening of connective-tissue supports in sprue seems to explain the great frequency of abdominal ptoses, especially of the stomach, which is frequently dilated. Ulcers of the stomach and duodenum are not infrequent. An interesting side-light on this complication is seen in the recent work of Askanazy on a species of Monilia as the causative organism of certain gastric and duodenal ulcers. The author reported the occurrence of

a severe hematemesis in the course of a case of sprue in 1913, and has since seen other instances of this disturbance.

Diagnosis.—*Laboratory diagnosis* is made by sowing feces, tongue scrapings, and (according to Wood in a personal communication) gum scrapings in Petri dishes on 2 per cent. Sabouraud glucose agar. Colonies resembling those of *Monilia psilosis* are fished after four or five days, isolated in pure culture, and subjected to the differential culture tests already mentioned. Serological tests require an antigen from virulent strains and the usual technic for the complement-fixation test.

Pellagra is more prone to invade the country districts and to attack the poor. In pellagra there is apt to be a normal absorption of fats, while in pronounced cases of sprue fat absorption is subnormal, and may often be as low as 50 per cent. of the amount ingested. Wood states that anemia is not a feature of pellagra. The classical skin lesions and involvement of the nervous system which are characteristic of pellagra are lacking in sprue.

In *pernicious anemia* the subcutaneous fat is preserved and the tongue is not so characteristically excoriated as in sprue. But many a pitfall awaits the hematologist who would presume to differentiate sprue from pernicious anemia by the blood-picture alone. Generally, however, there is an absence of nucleated red cells in the anemia of sprue.

Prognosis depends largely on the promptness with which a diagnosis is made, and on the constant maintenance of an obligatory diet. Given these two premises, sprue cannot be considered a very fatal disease. The cachexia of sprue, really a sequel of the disease, offers a serious outlook.

Treatment.—The vast majority of patients recover if fed on a diet with a low fat content which is free from cereals and the sugar of commerce. Eupeptics are of value, as is also calcium in the correction of a deficiency in this element. Without a strict limitation of the diet one can hope for little in the management of sprue.

We have much to learn concerning the size and coherence of the different starch molecules, as well as those of the various sugars, before any explanation may be found for the necessity of removing from the diet all commercial sugar and cereals, as well as certain starchy legumes and the major part of the fats. The digestive glands producing diastase and lipase must be allowed to recuperate, and the causative fungus deprived of a medium favoring growth for a period of not less than three months, and often of more than one year. Prohibited foods may then be cautiously administered as the functions of the diastase- and lipase-producing organs are gradually restored. In the cachexia of sprue, as a rule, only a milk diet can be tolerated, and in the majority of such cases adherence to this diet alone offers any hope for the patient. As protein digestion is generally undiminished in this disease the diet consists chiefly of milk, lean meat, eggs, vegetables, edible leaves, and fruits.

Vaccine Therapy.—*Monilia psilosis vaccine* is a 1 per cent. emulsion of killed and iodized cultures. Weekly subcutaneous injections may be used. The initial dose of 0.1 c.c. is increased gradually. The results are encouraging, but time and experience alone will establish the real value of vaccine treatment.

Prophylaxis.—A well-balanced diet, the avoidance of carbohydrate excess, sufficient repose, moderate exercise, and protection against excessive heat are the sum of preventive measures. Sour bread and sweet drinks

hawked about the streets have been found to contain *Monilia psilosis* and should be avoided. Reasonable care against contamination should be taken by persons exposed to sprue.

BAILEY K. ASHFORD.

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PSOROSPERMIASIS

Pathogenic psorosperms, which occur frequently in invertebrates, are uncommon in mammals, and seldom lead to serious disease in man. Perhaps the commonest psorosperm is "Rainey's tube," found within the sarcolemma of pig's muscle. It is ovoid and is filled with minute sickle-shaped unicellular organisms, *Sarcocystis miescheri*. Occasionally similar structures occur in human muscle, but the only psorosperm which is known to cause serious disease in man belongs to the coccidia.

COCCIDIOSIS

Definition.—Coccidiosis is a protozoan infection caused by the parasite *Coccidium oviforme*, in which there is proliferation and obstruction of the bile-ducts with subsequent formation of round whitish nodules and sometimes of cysts in the liver.

The *Coccidium oviforme* is a minute elliptical parasite, common in rabbits and mice, but rarely observed in man. It lodges in the columnar epithelial cells of the intestines or bile-ducts, and grows slowly until its size exceeds that of the cells themselves.

Symptoms.—The disease resembles that found under similar conditions in rabbits. Its rarity is indicated by the fact that only 6 cases are reported in the literature. The symptoms vary. The onset may be evidenced by slight fever and drowsiness, or may be more acute and simulate that of scarlet fever. The liver and spleen are usually enlarged, and there may be slight tenderness over them. These organs may contain caseous foci surrounded by congestion. In one case papule-like elevations, resembling tubercles, were noted in the ileum; these proved to be coccidia. The nodules caused by the parasites may simulate mucous cysts. Occasionally the parasites lodge in the kidneys and ureters and cause hematuria and frequent micturition.

Course.—The disease is apparently always fatal, death occurring about two weeks after the onset. Autopsy has revealed whitish neoplasms in the

peritoneum, omentum, pericardium, spleen, liver, kidneys, and ureters. The liver and spleen, however, are most commonly affected.

Treatment.—No successful treatment has been found.

RUSSELL L. CECIL.

AMEBIC DYSENTERY

(*Intestinal Amebiasis, Entamebiasis, Amebic Colitis*)

Definition.—Amebic dysentery is a specific infection of the large intestine characterized by discharges of blood and mucus. The symptoms are usually intermittent. Secondary lesions occur, principally in the liver. The causative organism is *Entamœba histolytica.*

There are many conditions in which more or less spasmodic diarrhea or dysentery may appear as an occasional symptom, but in two infections, namely, bacillary and amebic dysentery, the cardinal manifestation is an acute discharge of bloody mucus which is sustained over a long period. Bacillary dysentery is a fairly simple disturbance caused by a specific bacterium. Amebic dysentery has commanded the attention of workers in several fields because of its interesting etiology, its striking pathology, and the comparatively satisfactory methods of its diagnosis and treatment.

History.—Attention was first directed to amebæ as the possible cause of dysentery by Lösch in 1875, but his suggestion was not received very seriously on account of the occurrence of typical cases of dysentery without apparent amebic infection. Amebic dysentery was established as a definite entity in 1891 by the pathological studies of Councilman and Lafleur. The situation was greatly simplified about 1900, when the etiology of bacillary dysentery was fully established, but the fact that amebæ were frequently found in the stools of healthy people was still a complication to the problem. A definite step toward the clarification of this difficulty was taken by Schaudinn in 1903. He suggested that the amebæ commonly seen in the feces of man could be separated into two distinct species—a pathogenic and a non-pathogenic type. The former he named *Entamœba histolytica* on account of its ability to dissolve tissues; the harmless form, *Entamœba coli.* The details of Schaudinn's work on the morphology of *E. histolytica* have subsequently been extensively modified by Walker. The recognition of a non-pathogenic ameba in the intestinal tract of man was a fundamental step in establishing the etiological rôle of *E. histolytica* in one form of dysentery. It is necessary to understand the various types of amebæ occurring in the intestinal tract of man in order to appreciate their clinical significance. The main features are summarized in the accompanying outline, the conclusions of necessity being drawn more or less arbitrarily for presentation in tabular form.

TYPES OF AMEBÆ FOUND IN THE INTESTINAL TRACT OF MAN

Classical examples.	Occurrence.	Microscopical examination.		Parasitism in man.	Pathogenicity in man.	Infection of lower animals.	Cultivation.	Effect of emetin.
		Trophozoites in fresh preparation.	Cysts. No. of nuclei.					
Entamœba histolytica.	In feces and in tissues.	Active motility, ingestion of red cells, clear pseudopodia.	Typically 4.	+	+	+	+	+ (in man).
E. coli.	In feces.	Homogeneous granular protoplasm, sluggish motility.	Typically 8.	+	0	0	(?)	0 (in man).
Limax group.	Ordinarily not seen in feces.	.....	1 or 2.	0	0	0	+	+ (*in vitro*).

Etiology.—There is only one clearly established pathogenic ameba of man, namely, *E. histolytica*. Of the parasitic but non-pathogenic group, *E. coli* is the classical and the most important example. New amebæ are being described from time to time in this group, and protozoölogists still differ among themselves as to the exact number of species. In addition to *E. coli*, the better known examples are *Endolimax nana* and *Iodamœba butschlii*. The limax group of amebæ includes free-living forms found abundantly in nature which are occasionally taken into the intestinal tract with food and water. They do not colonize in the bowel, but some species are able to survive mechanical passage through the intestine. It is only by merest chance, however, that they are ever seen in the microscopical examination of freshly passed feces, but they often appear in cultures.

By experimental inoculation in man it has been demonstrated that limax amebæ and *E. coli* are non-pathogenic, though the latter parasitizes readily. Walker fed the pathogenic form, *E. histolytica*, to 20 volunteers, 18 of whom became parasitized, and 4 of these 18 contracted typical dysentery. The 14 remaining individuals developed no symptoms. It is clear from this experiment and from subsequent observations that a considerable number of individuals become carriers of *E. histolytica* without the appearance of any symptoms of dysentery.

As early as 1887 Hlava infected lower animals with *E. histolytica* and produced a typical acute dysentery. Amebic dysentery sometimes develops spontaneously in lower animals, particularly in dogs. It was formerly supposed that a strain of amebæ dies out after five or six subpassages in animals (kittens), but Baetjer and Sellards proved that this idea is groundless. The more important characteristic features of the human disease are reproduced typically in the lower animals even to the development of abscesses of the liver. As with most protozoa, the mode of action of the amebæ is not clearly understood. There is no direct evidence that the death of the host can be brought about by any toxic action of the organisms. Indeed, in kittens the immediate cause of death is usually a bacterial septicemia.

Schaudinn reported that *E. coli* readily parasitized young kittens without producing symptoms, but this result has not been confirmed.

The cultivation of *E. histolytica* was evidently first accomplished by Cutler. The methods of cultivation have been extended and improved by Boeck and Drbohlav.

Epidemiology.—Amebic dysentery is characteristically an endemic disease of tropical and subtropical climates, but it also occurs occasionally in the colder parts of the temperate zones. The cysts are undoubtedly the propagative stage of the entamebæ. For an obligate parasite to propagate itself successfully in nature it is obviously necessary that it be able to leave the body of an infected host and set up a new infection in a normal individual. This process is simple in the case of the amebæ. The vegetative and encysted forms are excreted in the feces. No multiplication takes place outside of the host. Indeed, the trophozoites degenerate rapidly, often disintegrating within a few hours. The cysts are much more resistant and, on being ingested with food or drink, they readily set up new infections, with or without the development of symptoms. Individuals who have never had symptoms of dysentery, but who are constantly passing virulent cysts, are a serious menace to their associates.

The vegetative forms when ingested by man seldom set up an infection,

since they are easily destroyed by the digestive juices. From a practical standpoint, however, full precautions must be taken in handling the dejecta of a patient passing only vegetative amebæ, since cysts may appear in the stools at almost any moment.

The stimulus in the intestinal tract which excites excystation of the entamebæ is unknown. Certainly warmth and fluid are necessary. Nutrient matter and enzymes, singly or in conjunction with each other, may be essential factors. After the ingestion of cysts the exact details of the early process of the infection are not clear. It is assumed that excystation takes place somewhere in the small intestine, giving rise either to a single amebæ with 4 nuclei or very possibly to 4 amebulæ, each with a single nucleus. In any case the newly hatched organism is carried along by peristalsis till some point of stasis is reached in the large bowel, such as the flexures of the colon. At such points, injury of the mucous membrane by the amebæ often takes place and results in invasion of the tissues.

Morbid Anatomy.—The primary lesions are confined to the large bowel; ulcerated areas are found throughout its entire extent in about one-half of the patients coming to autopsy. It is particularly in long-standing cases that this extensive ulceration develops. Not uncommonly one finds the lesions restricted almost entirely to the cecum and ascending colon, with or without involvement of the sigmoid and rectum. Less often the lower portion of the bowel alone is involved. Occasionally the lesions extend from the cecum into the appendix. Rarely, in advanced cases, secondary invasion of the lowest portion of the ileum has occurred. From experiments upon lower animals it seems probable that the ileocecal valve affords considerable mechanical protection to the ileum against migration of amebæ from the cecum.

Ulcerative bacillary dysentery produces an acute diffuse inflammation, while in amebic dysentery, even in advanced cases, islands of normal mucosa are found in the affected areas.

It seems clear that the amebæ are able to injure and penetrate the normal mucosa and then rapidly invade the submucosa, the overlying mucosa necroses leaving an ulcer with deeply undermined edges. Microscopically, amebæ are seen in great numbers and often invade the blood-vessels. It seems probable that they are frequently carried to the liver, but that only a small proportion are able to gain a foothold and set up hepatic lesions. The lesions of the liver vary in detail. Multiple abscesses may occur, but usually a single abscess is found which may ultimately attain a relatively enormous size, and rupture into the peritoneal cavity or through the diaphragm into the lung. There is no predilection for any given lobe of the liver, but as the right is the larger it is involved more often than the left.

The amebæ first of all produce necrosis of the liver with but little disturbance in the surrounding tissue. The impression prevails that they usually occur in pure culture in the abscesses. The intestinal bacteria are, however, frequently found, though *E. histolytica* is the only pathogenic organism which is constantly present. The invading bacteria modify the reaction in the surrounding tissue and the character of the contents of the abscess. Liquefaction of the contents may be delayed for a long time and consequently it may be difficult to locate an abscess by aspiration. The invading bacteria are largely responsible for the reaction in the surrounding tissue. The wall of the abscess consists of granulation tissue. As would be

expected, the amebæ are found in this wall and not in the necrotic center of the abscess. Consequently the pus which is drawn off at operation usually fails to contain amebæ, but after a few days the organisms make their appearance in the discharge from the granulating wall.

Symptoms.—The *incubation period* is variable and difficult to estimate. As determined experimentally by Walker in man, after the ingestion of cysts, amebæ appear in the stools within a few days (usually four to six), though the extreme limits of the incubation period are very wide. In 4 experimental cases the interval elapsing between the appearance of amebæ in the stools and the development of symptoms ranged from nine to ninety-four days. The *onset of symptoms* may be sudden or gradual. In contrast to Asiatic cholera, the bowel movements are accompanied by a moderate degree of tenesmus and abdominal pain. There is usually no nausea, and the appetite remains unaffected. If the patient is untreated, the symptoms usually subside more or less completely in a few weeks only to reappear again. Indeed, a history of intermittent attacks of dysentery at once directs suspicion toward an amebic infection. These untreated patients may become carriers, but more commonly a chronic diarrhea develops. The invading bacteria eventually play a prominent part in the symptoms. Periods of low fever and leukocytosis appear from time to time. The patients become anemic and emaciated and are slowly but steadily exhausted in a few years.

Fulminating cases with signs of marked toxemia have occurred in the tropics. Death may take place during the first few days of the disease as the result of intestinal hemorrhage or perforation or from bacterial complications.

Complications and Sequelæ.—With the improvement in diagnosis and treatment, invasion of the liver is apparently becoming less common. Abscess of the liver has been noted in carriers who have never showed any signs of intestinal symptoms, and also in patients long after the intestinal symptoms have subsided. Secondary metastatic infection of other viscera has been observed; for example, the development of abscesses of the brain and spleen. Armitage found reports of 48 cases of brain abscess in the literature.

Mixed infections with bacillary and amebic dysentery may occur, but are not common. The author has on several occasions seen amebic dysentery develop during an attack of typhoid fever.

In the healing of extensive lesions of the intestine, the excessive formation of scar tissue sometimes leads to partial obstruction. A child of fourteen years, with a giant colon who was thought for a time to have Hirschsprung's disease, proved ultimately to have an amebic infection of about nine years' standing.

Immunity.—As in the case of most protozoan infections an acute attack of amebic dysentery affords no protection against subsequent infection. Indeed, relapses are the rule in an infection of the intestine with amebæ. The amebic infections of the liver show no tendency to recur.

Diagnosis.—The clinical syndrome of an acute attack of amebic dysentery is surprisingly similar to that of the bacillary type. It is remarkable that two very different parasites—one a highly organized protozoön, the other a simple bacterium—can produce symptoms which are almost indistinguishable. In general, the bacillary patients appear somewhat toxic and may

show some fever and leukocytosis, but these features are by no means sufficiently marked to permit clinical differentiation. Physical examination of an amebic patient with moderate symptoms reveals little except abdominal spasm and tenderness over the affected portions of the bowel. The temperature is normal or slightly elevated, especially in the afternoon. The pulse may be slightly increased in rate, but is almost unaffected in volume and tension.

One must watch carefully for the possibility of involvement of the liver. An abscess high in the dome may produce few physical signs. An advanced lesion may lead to weakness and anorexia, the development of fever, and leukocytosis accompanied sometimes by chills and sweating. *x*-Ray plates seldom reveal an abscess of the liver, but fluoroscopy is of value in revealing limitations of motion of the diaphragm when the abscess is near the upper surface of the liver. Exploratory aspiration is commonly practised.

The entire course of the disease is naturally more characteristic than merely the symptoms of an acute attack. An intermittent dysentery accompanied by abscess of the liver constitutes a characteristic clinical picture. In the differential diagnosis, one must take into consideration the intestinal symptoms which arise in diseases such as schistosomiasis, tuberculosis, carcinoma, and also syphilis of the rectum.

Microscopical Examination.—In the differentiation of bacillary and amebic dysentery, the gross appearance of the stools is important. The bacillary type of disease usually commences acutely. The fluid stools contain but little fecal matter, a moderate amount of mucus, and often considerable blood which may be partially laked. Microscopically, many pus-cells are seen together with large and small mononuclear cells; the latter are sometimes phagocytic and may, superficially, resemble amebæ.

In amebic dysentery, on the other hand, the stools usually contain considerable fecal matter mixed with blood and mucus. The cellular exudate is ordinarily less abundant than in the bacillary disease.

These secondary aids to diagnosis are emphasized, because in the clinical management of patients with bacillary dysentery it is necessary to make a provisional diagnosis before the bacteriological examinations can be completed. If no entamebæ are found and if the stools are characteristic of bacillary dysentery, then a specimen should be taken for bacteriological examination, and treatment with antidysenteric serum begun. In the meantime the examinations for amebæ must be continued. Since the organisms degenerate very rapidly outside the body it is necessary that fresh stools be examined. In cold climates there is no need of keeping the stool warm during its transportation from the ward to the laboratory. Outside of the body, the amebæ degenerate less rapidly in the cold, and they readily resume their motility on being warmed.

Thorough familiarity with the morphological details of the entamebæ requires expert training in the field of protozoölogy. The two entamebæ, namely *coli* and *histolytica*, are not strikingly different in their vegetative stage. They measure approximately 20 to 30 micra in diameter. The nucleus of each is small in proportion to the size of the cell and very poor in chromatin. *E. histolytica* presents evidence of greater motility. The ectosarc is clear and hyaline, and phagocytosis is active, the amebæ often being filled with red cells, but seldom with bacteria. *E. coli* is usually sluggishly motile, contains no red cells, but ingests bacteria. In typical

cases the differentiation of the trophozoites of the two forms is easy, in borderline cases difficult or impossible. The cysts of *E. coli* are fairly large (approximately 15 micra in diameter), and typically contain 8 nuclei. The cysts of *E. histolytica* vary in size (7–15 micra) and typical forms contain 4 nuclei. Super- and sub-nucleated forms of both species occur. *Endolimax nana* in its vegetative stage is smaller (10 micra) than either of the two entamebæ just described and the nucleus contains a mass of chromatin arranged in a large eccentric karyosome. The typical cyst is ellipsoidal in form and contains four nuclei.

Prognosis.—Of the early cases, approximately one-third are cured by a single complete course of emetin. The patients who relapse have a good outlook for recovery if the relapses are treated persistently and thoroughly. After extensive bacterial infection of the intestine has taken place the patient is fortunate if he ever recovers his full health.

Prophylaxis.—There is no method of specific protection against amebic infection. Personal measures depend upon the usual hygienic precautions and cleanliness of the individual.

Treatment.—During the acute stage the patient must be at rest in bed. The *diet* should be bland, but the amount may be liberal if the appetite is good.

Emetin, which has become the standard drug for specific treatment, may be administered as the hydrochlorid, either in intramuscular injections of 1 grain per day or in the form of salol-coated pills ($\frac{1}{2}$ grain per day). This course of treatment should be continued for twelve days. Of late years the impression has gained ground that emetin is more effective when given by mouth than when injected parenterally. A compound, emetin bismuthous iodid, which contains about 30 per cent. of emetin, has been prepared for oral use. It is almost insoluble in neutral or acid solution, but dissolves readily in the alkaline contents of the duodenum. The usual dose is 3 grains daily for twelve consecutive days. Notwithstanding its extremely slight solubility in the gastric contents, some nausea usually follows its administration and vomiting frequently results. This disadvantage is outweighed by the fact that emetin bismuthous iodid is the most effective form of routine therapy which is available at present.

The margin between the effective and the therapeutic dose of emetin is small. In a single course of treatment the maximum dose of 18 grains should not be exceeded. The drug is by no means harmless and constant lookout for indications of poisoning must be kept—the principal signs being the development of peripheral neuritis, diarrhea, an increase in the pulse rate, and a loss in weight.

In early cases the immediate effect of emetin treatment is often brilliant, the dysenteric symptoms ceasing within a few days and the amebæ disappearing from the stool. Relapses, however, are extremely common.

The plant *Castela nicholsoni* contains an active principle, probably a glucosid, which is very valuable in the treatment of amebic dysentery. Therapeutically, castela is equal or even slightly superior to emetin. Moreover, it can be used easily and safely by oral administration, and patients tend to gain rather than lose weight while under treatment. Unfortunately, reliable preparations of this plant are not yet available commercially.

The neglected amebic cases of several years' standing respond very poorly indeed to treatment with either emetin or castela. These drugs may fail to give even symptomatic relief in old chronic cases, or, if the symptoms

and amebæ disappear, relapses are prone to occur within a week after cessation of treatment. It is of extreme importance, therefore, that amebic patients be treated early and that relapses should have prompt and careful attention.

The question of surgical intervention inevitably arises when there is failure to respond to medical treatment. An appendicostomy is sometimes performed, but the most generally satisfactory type of operation is an ileostomy or colostomy, which permits the large bowel entire rest.

Liver Abscess.—Early lesions of the liver sometimes heal under treatment with emetin. Occasionally the abscess may be aspirated and a dilute solution of emetin injected into the cavity. Unless definite improvement takes place, a radical operation must be performed to establish free drainage. The operative risk is very great (30 to 60 per cent. mortality).

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MALARIAL FEVER

Definition.—Malarial fever is an infectious disease characterized by paroxysms of intermittent fever which may occur daily (quotidian), every other day (tertian), or every third day (quartan), or be continuous with marked remissions. Less commonly a pernicious, rapidly fatal form, or a chronic type with anemia and enlarged spleen, are observed.

History.—Hippocrates gave a good description of the quotidian, tertian, and quartan types of intermittent malarial fever. What is believed to have been malaria was described in the writings of Plautius about 184 B. C.

The discovery, about the middle of the seventeenth century, of cinchona bark and its use in malarial fevers was an important event in the history of this disease. Thereafter fevers were divided into two classes: those which were cured by the bark, and those which were not. Quinin was isolated by Pelletier and Couventou in 1820.

In 1880 Laveran, a French Army surgeon, discovered the malarial parasite within the red corpuscles of patients suffering from malaria. Five years later Marchiafava and Celli increased our knowledge by a most accurate description of the parasite, and Golgi observed that parasitic sporulation and fever coincided. Sternberg, Councilman, Abbot, and Osler were among the first in the United States to appreciate the significance of Laveran's work. Ross studied the problem in India and showed that the parasites developed in the body of the mosquito. Practical demonstrations by Italian workers and experiments on Manson, Jr., determined that the disease was transmitted directly to man by the bite of infected mosquitoes.

Incidence.—Malaria is most prevalent in a belt which extends approximately from south latitude 20 to north latitude 35. The incidence declines rapidly as civilization advances, and the disease has already disappeared almost entirely from many countries where it was once prevalent. A hundred years ago malaria was common in Germany, France, and England; now it is rare. Fifty or seventy-five years ago malaria was one of the most important diseases in the large centers of the New England states, Maryland, Ohio, and southern Illinois. Now it occurs in these regions in a very mild form and in limited areas. In the southern states, where it is still common, the severity, incidence, and extent of the disease is rapidly decreasing. If this present rate of decline continues there will be little malaria in the United States by 1935 or 1940.

In the warm countries nearest the equator and wherever the annual rainfall is large, malaria is still very prevalent. The infection rate varies from zero to practically 100 per cent. of the population. There are vast areas inhabited by millions of people in India, Africa, Burma, Russia, China, and South and Central America, where the morbidity and mortality from malaria is enormous.

Etiology.—Malaria is caused by certain species of protozoa: the *Plasmodium vivax* (the tertian parasite); the *Plasmodium malariæ* (the quartan parasite); and *Plasmodium falciparum* (the estivo-autumnal parasite). Malarial parasites belong to the division Protozoa, the class Sporozoa, and the order Hemosporidia. These are closely related, but each possesses definite morphological characteristics and gives rise to a unique syndrome. There are at least two or more subdivisions of the estivo-autumnal parasites. Some authorities believe that these are entirely different species.

The plasmodium is introduced into the body of man by one or the other of these species of mosquitoes. It exists in two forms: the *parasite* in man, who is the intermediary host, and suffers symptoms of malaria; and the *extracorporal form* which lives and develops in the mosquito, which is its definitive host. Although there are at least three distinct parasites, they all live, grow, and reproduce in the body of man in a similar manner. The life cycle of all is much the same.

The Parasite in Man.—The youngest form of the parasite in man consists of a small mass of protoplasm with a nucleus rich in chromatin, which stains with any modifications of the Romanowsky polychrome stain. These young parasites, the merozoites, are first attached to the red blood-cell, later situated within it. The smallest are from one-fifth to one-tenth the diameter of the erythrocyte. Some of them, particularly the tertian, are ameboid and irregular, but others are more regular. When stained, they appear as small "signet rings" within the red blood-cell.

The parasite gradually increases in size, and after twelve to fifteen hours small brownish granules of pigment can be seen in the parasite. In fresh wet preparations this pigment is actively motile. Apparently, the substance of the erythrocyte is consumed as the parasite grows, probably because it serves as nutriment to the parasite. As growth progresses, more and more pigment is produced, and the nucleus first becomes polymorphous and later divides into several parts. At the end of the developmental period, which varies from thirty to seventy-two hours in the different types, the parasite has attained a size almost equal to that of the erythrocyte, which is reduced to a thin shell or capsule around the parasite. In suitable preparations the

parasite at this stage can be seen to be divided into a number of subdivisions, each of which has its own small nucleus; all are still contained within the capsule in which development took place. Such mature forms are called "*rosettes*," and consist of organisms that have matured and divided by segmentation into a number (8 to 32) of young parasites or merozoites.

The capsule containing the mature parasite ruptures, and sets free the merozoites, each one of which can attach itself to another erythrocyte and, by repeating this cycle, produce other merozoites. Fortunately, however, most merozoites that are set free are destroyed by phagocytes and by antagonistic substances in the blood, and only a small proportion succeed in attaching themselves to red blood-cells and thus escape destruction. The prevalent impression that malarial parasites pass their entire life cycle in the circulating blood is incorrect; most of their life is spent in capillaries and not in the circulating blood. The capillaries of the bone-marrow and spleen, where the current is slowest and the force weakest, contain the largest number of parasites.

There is a tendency for asexual reproduction of large groups of the malarial parasites (schizogony) to take place at one time. Those that mature on a given day tend to do so at the same time of day. The quartan parasite develops in about seventy-two hours, the tertian in forty-eight hours, and the estivo-autumnal in twenty-four to forty-eight hours.

After an individual has had symptoms of malaria for several days, careful examination of the blood may reveal, in addition to the asexual parasites, others which are sexually differentiated. Observers who are familiar with these can distinguish the male and female. These sexual parasites are called gametocytes or, more commonly, gametes. The tertian and quartan forms are round or oval, irregular in outline, and ameboid; the estivo-autumnal gametes are oval or crescent shaped, and very slightly ameboid. Gametes do not reproduce in the body of man and do no harm there. They die within one to three weeks, but, of course, new gametes may be constantly developing in the blood. The influences that govern their development are not definitely known. Not all persons who have malaria have gametes.

The differential characteristics of the three species of malarial parasites are shown in the following table:

	Estivo-autumnal.	Tertian.	Quartan.
Schizonts in the peripheral blood.	Rings only.	All sizes.	All sizes.
Shape of gametocytes.	Crescentic and oval.	Round or oval.	Round or oval.
Shape of outline of schizonts in peripheral blood.	Rings. May have two chromatin granules.	Irregular after ring stage is passed.	Regular after ring stage is passed.
Influence upon color of erythrocyte.	Not changed.	Faded, pale.	Darker. Normal red color intensified.
Influence upon size of erythrocyte.	Not changed.	Enlarged.	Reduced.
Pigment in schizonts and gametocytes.	Medium to coarse.	Very fine.	Coarse.
Schüffner's granules.[1]	.....	Often present.	Not present.
Number of segments in rosette.	.....	32.	8.
Period of asexual development.	.....	Forty-eight hours.	Seventy-two hours.

[1] Red staining granules in the erythrocyte containing the parasite.

If blood containing gametes is drawn into the stomach of an Anopheles mosquito, sexual reproduction takes place. The male microgametocytes throw out long flagellæ, which soon break off and move about in the fluid. Such a microgamete penetrates a female (the macrogametocyte), which is then fertilized, and initiates a cycle of reproduction. The fertilized zygote in the stomach of the mosquito becomes actively ameboid, passes through the stomach wall, and lodges on the outer surface of the stomach within the abdominal cavity. There it rapidly develops to many times its original size. At the end of the developmental period (fifteen to twenty-five days) it has grown into a large oöcyst which contains many spindle-shaped bodies, each of which consists of a small amount of protoplasm and a nucleus. The cyst ruptures and sets free into the abdominal cavity these young parasites called *sporozoites*. Some are carried to the salivary gland of the mosquito and introduced into the blood of the next person bitten. They enter the red blood-cells of the human host, grow, reproduce, and give rise to clinical symptoms, usually in about fourteen days. *Anopheles quadrimaculatus* seems to be the chief carrier of malaria in America, but other mosquitoes are more important in some parts of the world.

Only the female mosquito bites, and each one tends to return for subsequent blood meals to the place where the first was obtained. Consequently a patient with malaria is a greater menace to the health of those living under the same roof than to that of other people.

Morbid Anatomy.—Individuals who have died from malaria usually have a dusky, brownish hue because of the anemia and the pigmentation of the skin.

The *spleen* is always enlarged in proportion to the duration of the disease and the type of infection. Tertian fever causes the greatest enlargement, estivo-autumnal, least. It is grayish and reddish brown, "light chocolate to black" (Craig). The capsule is smooth and thin. The cut surface varies from slate color to almost jet black, on account of the presence of a large quantity of pigment. The pulp is very soft and the malpighian bodies usually stand out noticeably. Microscopical examination shows that the vessel walls are thickened, and that the lumen is frequently obliterated by enormous numbers of parasites, both free and within the endothelial cells lining the vessel. Smears of pulp contain enormous numbers of parasites, red-cell débris, and pigment, much of which is within the mononuclear cells. In the spleen of individuals who have died from other diseases, but who had associated latent malaria, parasites and pigment are always present. The spleen may or may not be enlarged.

The *liver* is always enlarged and congested when death is due to malaria. The degree of discoloration varies with the pigment content. Microscopically, many of the capillaries are seen to be plugged with pigment and parasites. These are particularly likely to be contained in the endothelial cells lining the vessel. When death follows other diseases in the presence of latent malaria, pigment and parasites can be found in the liver, but not in such quantities as in the spleen.

The *kidneys* are congested, the capsule strips easily, and the medullary pyramids sometimes contain minute hemorrhages. The capillaries may be plugged with parasites. There is more or less cloudy swelling of the cells lining the convoluted tubules, some of which are plugged with casts. In hemoglobinuria the tubules, especially the loops of Henle, are usually ob-

structed with casts of hemoglobin and detritus. Complete occlusion of the tubules with casts explains the urinary suppression which nearly always occurs in fatal cases.

The *brain*, especially in the cerebral types of malaria, is frequently of a grayish or slate color owing to the presence of malarial parasites in its capillaries. Hemorrhages and thrombi are often noted. Smears or contact preparations demonstrate that the capillaries are plugged for long distances with parasites in all stages of development, thus accounting for the coma of cerebral malaria.

The entire *vascular system* is affected in malaria. Capillaries throughout the entire body contain parasites and pigment, and many are obstructed for long distances. The endothelial cells, even in the larger vessels, contain parasites and pigment. No doubt much of the damage caused by malaria is due to interference with the circulation in vital organs and tissues by blocking of the small vessels.

The *bone-marrow* is discolored and the small vessels are filled with malarial parasites and pigment; the macrophages, with pigment alone.

Pathogenesis.—The theory of Baccelli, that the fever in malaria is caused by a toxin produced by the parasite, is rather generally accepted, but has never been definitely proved. Craig states that in the light of our present knowledge we must conclude that the rise of temperature in all malarial fevers is due to a toxic substance or substances produced by the plasmodia during their development, and liberated at the time of sporulation of these organisms. If a sufficient amount of this toxin is set free suddenly, there is a general relaxation of the entire vascular system, so that much less blood passes through the capillaries, especially those of the skin. The surface of the body then assumes the temperature of the surrounding air, is cooled, and the patient has a chill of variable severity and duration.

Until the toxin is neutralized or eliminated it causes an elevation of temperature. The neutralization or elimination usually occurs within a few hours in intermittent fever, in which the parasites reproduce by groups; but in remittent or continued malarial fever, in which the parasites reproduce continuously, the temperature may remain high for longer periods.

In some cases the parasites tend to localize in certain organs and tissues, and thus give rise to symptoms directly referable to those organs; choking of the capillaries of the brain causes cerebral malaria. Capillaries are obstructed more markedly by the estivo-autumnal parasite than by the other forms, and, consequently, there are more fatal cases in this type of malaria.

It is not known just how or why hemoglobinuria occurs in some cases of malaria. Only certain individuals are susceptible and, although malaria alone may cause it, administration of quinin often hastens its development.

Symptoms.—The symptoms of malaria vary widely, but fall into two rather definite groups: (1) those of the regularly intermittent fevers; and (2) those of remittent or continued fevers.

(1) *Regularly Intermittent Fevers.*—In the tertian and quartan forms of malaria there are recurrent paroxysms, commonly called ague, in which, as a rule, chill, fever, and profuse sweating follow each other in orderly sequence. The period of incubation is uncertain. Experimentally it varies from thirty-six hours to fifteen days. A definite aura usually precedes *the chill*, the patient being made aware of its advent by headache and uneasy sensations. Yawning, lassitude, and even nausea and vomiting may also

precede it. Fever actually begins before the chill, but is often not detected unless the rectal temperature is taken. Gradually the patient begins to shiver, and the fully developed rigor may be so severe as to shake the bed. The skin becomes blue and cold, and a surface thermometer will indicate a reduction of the skin temperature. Axillary and rectal temperatures may increase to 106° F. during the actual chill. In children delirium and convulsions occur. The chill may last from a few minutes to an hour or more.

The Fever (Hot Stage).—The coldness of the skin gradually disappears and the skin becomes intensely hot. The face and body are flushed, the pulse is full and bounding. Throbbing headache and active delirium are often present. Thirst is extreme. This stage lasts from thirty minutes to four hours.

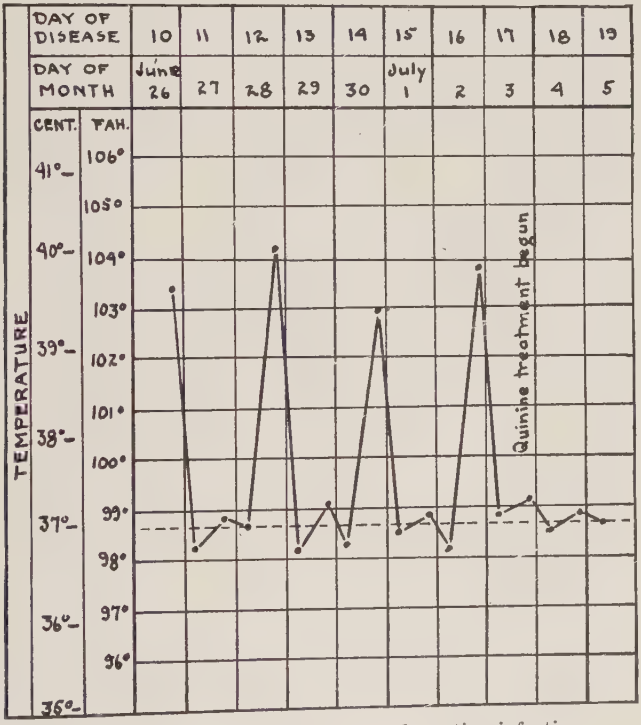

Fig. 8.—Temperature chart of single tertian infection.

Sweating Stage.—Sweating may vary from slight perspiration to a severe sweat. Following this stage the patient feels much better, usually drops into refreshing sleep, and is often able to be up until the advent of the next paroxysm.

The paroxysms occur at about the same time of day in any given case, more in the morning than in the afternoon, and almost never at night. When the disease is in its incipiency they occur earlier each time; but when the disease is wearing off, they occur later each time.

The three stages consume from ten to twelve hours. Variations are common. A slight chilliness only may be present. The hot stage alone, or with only slight sweating, may constitute the entire cycle. During the

paroxysm the spleen is enlarged and the edge can usually be felt below the costal margin.

Tertian fever depends upon the presence of the tertian parasite, whose cycle of development lasts about forty-eight hours, segmentation occurring every third day. There may be two groups of tertian parasites maturing on alternating days, thus giving rise to a paroxysm every day. This is known as *double tertian infection.*

In cases of *quartan fever* the paroxysms correspond to a parasitic cycle which takes seventy-two hours to develop. If the infection is single, paroxysms will occur every fourth day; if double, there will be two paroxysms, followed by a day of intermission; if triple, the fever becomes quotidian.

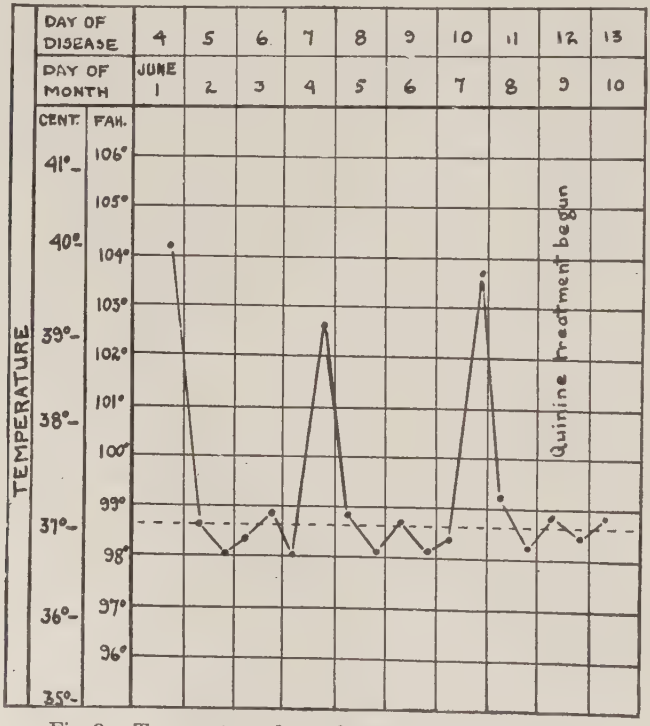

Fig. 9.—Temperature chart of single quartan infection.

The symptoms of quartan fever are milder than those of tertian, but the condition is prone to relapse, even after persistent treatment.

(2) *Remittent Fevers.*—Not all patients with malaria have definitely intermittent fever. Some, after one or more chills and attacks of fever, have continued or remittent fever, during which the temperature does not fall to normal, although it varies from time to time. The estivo-autumnal type, caused by the *Plasmodium falciparum,* is the most common of the remittent fevers. This type is observed in temperate climates, principally in the late summer and autumn; hence the term. The life cycle of the parasite is about forty-eight hours, but is subject to considerable variations, and thus produces irregular symptoms. Occasionally this fever may be confused with the quotidian type found in double tertian or triple quartan infection.

More often the paroxysms last over twenty hours instead of ten or twelve. The onset is frequently without chills, and the rise in temperature slow and gradual.

Pernicious Malarial Fever.—This type is always associated with the estivo-autumnal parasite. In the various severe conditions, usually classed as pernicious malarial fever, the restraint upon the reproduction of the parasite is decreased, or the parasites are localized in vital organs. The so-called "congestive chill" is merely a very severe paroxysm caused by unusually large numbers of parasites. Three forms of pernicious fever are observed—the comatose, the algid, and the hemorrhagic.

In *comatose malaria* the patient is struck down with symptoms of severe disturbance of the central nervous system, delirium, and rapidly develop-

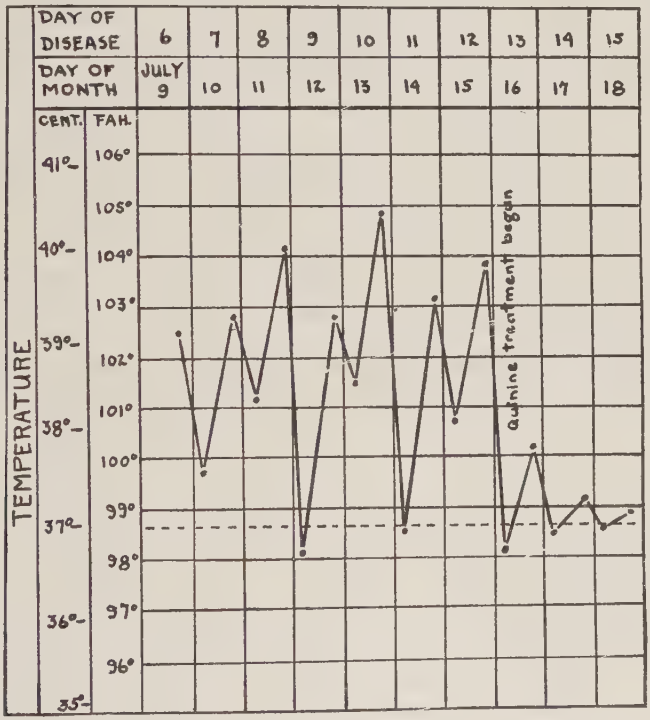

Fig. 10.—Temperature chart of tertian estivo-autumnal malaria.

ing coma. Chill may be absent. Fever is usually high. Unconsciousness may persist from twelve to twenty-four hours, or the disease may terminate abruptly. In these cases the symptoms are directly attributable to the presence of parasitic thrombi blocking the cerebral capillaries. More than 50 per cent. of fatal cases of malaria are of the cerebral type. The prognosis is always uncertain until after the patient has come out of the coma, and has been cinchonized.

In certain types of malaria profound gastro-intestinal disturbances are prominent; and in one, *the algid form*, subnormal temperature and profound prostration often lead to death from profound asthenia. This has been called the asthenic or adynamic form of the disease. In the cases with

vomiting and diarrhea there is often invasion of the gastro-intestinal mucosa by the parasite, resulting in thrombosis and ulceration.

Hemorrhagic Forms.—Malarial hemoglobinuria is noted in certain cases in which hemolysis of the red blood-cells takes place. In some instances this is due to the enormous number of red cells destroyed by the parasite. Frequently there is suppression of the urine. Hemoglobinuria occurs practically only when repeated attacks of malaria are poorly or insufficiently treated. The chill is usually severe and very weakening and depressing. The temperature is not often high. With the occurrence of the chill or soon after, the urine becomes deep red or almost black. The patient is greatly depressed and very ill. The urine may get darker and darker or become normal after a day or two. A second chill is usually accompanied by return of the hemoglobinuria. Malarial parasites may not be present in the blood after the first twenty-four or forty-eight hours. In persistent cases profound anemia and cachexia develop rapidly, and suppression of urine with resultant coma may lead to death. Observations in the Panama Canal Zone have led to the opinion that quinin should be withheld in cases of true erythrolytic hemoglobinuria, as it seems to favor hemolysis.

Malarial Cachexia.—This condition is characterized by dyspnea on exertion, swelling of the ankles, and hemorrhages, particularly into the retina. The temperature rarely rises to more than 100° F. The spleen is enlarged. Prognosis is usually good.

Although malaria ordinarily produces characteristic symptoms, its clinical manifestations are frequently atypical, and do not even suggest the nature of the infection. The disease may be latent and produce no symptoms. Examination of the blood for malarial infection is, therefore, essential in all acute and many minor illnesses which develop in malarial regions.

The extreme anemia brought about by malaria is in great part due to the mechanical destruction of the corpuscles by the parasites. The red corpuscles may be reduced to less than a million per cubic millimeter, and tend to be rather small and pale, or poor in hemoglobin; they also show some irregularities in size or form. Megaloblasts are seldom seen. The leukocytes are decreased. Another factor besides the actual red blood-cell destruction by the parasite contributes to the development of some of the severe malarial anemias. This is the action of the lysin already referred to, which has a predilection for the hematopoietic centers, such as the bone-marrow and spleen; as a result the anemia is more intense. A definite hemolytic agent is also a factor in the production of the severe anemias. It has been thought that quinin was a necessary factor in the production of such a state, especially in the blackwater fever type.

Relapse.—It is difficult to distinguish between relapses and reinfections. The former may occur for about three years after the initial infection. Quartan fever not infrequently will clear up spontaneously; or yield to quinin medication; but even after energetic treatment there is a peculiar tendency to relapse. Relapses following estivo-autumnal fever are uncommon. The symptoms in case of relapse are similar to those of the first attack. If quinin is not administered the patient becomes more anemic and weakened, the spleen enlarges, sometimes to enormous size, and the attack may last for weeks or months.

The cause of relapse in malaria is unknown, but the most plausible of

the various theories presented is that a special parthenogenetic form of the parasite may remain latent for an indefinite period, and any condition which reduces the individual's immunity (such as fatigue or overheating in the tropical sun) favors relapse, even under conditions that preclude the possibility of reinfection.

Complications.—Peripheral neuritis may lead to paraplegia, and hemiplegia sometimes complicates the pernicious comatose form of malaria. Multiple gangrene, orchitis, acute ataxia, and rarely, disseminated sclerosis are other possible complications.

Diagnosis.—The diagnosis of active malaria is usually easy and certain. An enlarged spleen is taken as a malarial index in a community which is infested. An absolute diagnosis is based upon the blood-picture, and the finding of parasites within and outside of the red corpuscles. Added confirmation can be obtained from the locality, the patient's history and symptoms, and the course of the disease—chill, fever, and sweating in chronological order. In cases of intermittent fever which do not respond to quinin therapy, even though the symptoms seem characteristic, malaria must be excluded as the cause.

The number of parasites in the peripheral blood in intermittent fever is greatest during the first six or eight hours after the chill, but some are always present. Occasionally the number of parasites in the circulating blood following the first or second chill is very small; in such instances the demonstration of parasites may be difficult. Practically speaking, however, chills and fever not associated with parasites in the blood cannot be attributed to malaria. In cases of latent malaria and in the interval between attacks parasites may or may not be found in the blood, or they may be present only intermittently. Therefore repeated examinations on successive days are necessary in ruling out the possibility of malarial infection. It should be emphasized, however, that parasites are not always demonstrable in cases of latent or receding malaria.

The therapeutic test with quinin, mentioned above, is of great negative but little positive value. The fact that a fever stops during the administration of quinin is not proof that it was due to malaria. This test should not be made except when it is impossible to examine the blood satisfactorily, for if quinin is given before the diagnosis is made, and the symptoms disappear, the diagnosis remains uncertain, and yet the patient is likely to be subjected to a long course of treatment on the assumption that he is suffering from malaria.

Associated Conditions and Differential Diagnosis.—In regions where malaria is prevalent it is often associated with other infectious diseases; but since malaria develops most frequently in warm climates, it is more likely to accompany hookworm and the parasitic infections common to such climates. Latent malaria often becomes active after surgical operations, injuries, and childbirth. Infected individuals, who have apparently been in good health for months, may develop symptoms of active malaria immediately after such incidents.

Slight jaundice may occur in long-continued tertian and estivo-autumnal infections, and, with the associated irregular pyrexia, may suggest hepatic abscess. The leukocyte count and examination of the blood for parasites will serve to differentiate the two. Jaundice may also result from malarial cirrhosis.

Whether blackwater fever is due to the effects of quinin in a patient whose blood is already susceptible to hemolysis on account of malaria, or whether it is a distinct malady, is not known.

An enlarged spleen, severe anemia, and pyrexia may be due to kala-azar, a disease observed in India. This condition may be distinguished from malaria by demonstrating the Leishman-Donovan bodies in the fluid obtained from splenic puncture.

Bacillary dysentery, septicemia, typhoid fever, acute endocarditis, and yellow fever must also be considered in differential diagnosis.

Prognosis.—The prognosis in malaria depends chiefly on early and thorough medication, and is usually excellent. Practically 100 per cent. of patients with ordinary mild malaria recover if treatment is thorough. In fact, in many untreated cases death does not result. Only those patients die who have not received proper treatment, or in whom the disease was too far advanced before treatment was begun. The outcome of pernicious malaria is always uncertain, especially if there is coma; the possibility of recovery cannot be assured until this state has passed and the patient is fully under the effect of the quinin. Hemoglobinuria also renders the prognosis uncertain. Tertian and quartan fever are rarely fatal. Death is usually caused by infections of the estivo-autumnal type. Probably the least favorable type is the rapidly fulminating comatose form in which there is a special localization of infection in the brain. Cases in which lesions have been produced in the spinal cord are not favorable to treatment.

In an attempt to estimate the malarial death rate in Sunflower County, Mississippi, where the incidence of this disease is particularly high, the author has recently obtained the following figures: The average number of cases treated during the years 1914 to 1918, inclusive, was 8236, and the average number of deaths annually was 77, a mortality of 0.93 per cent. A considerably larger number of persons had malaria, but were not treated. Inclusion of these in the figures reduces the mortality to 0.35 per cent.

Individual susceptibility influences the prognosis considerably. A person who has lived in a malarial region and has probably had malaria from time to time all his life, usually develops only a mild type. The disease is much more severe in those who have not been previously exposed.

Prophylaxis.—Inasmuch as malaria is conveyed solely by the bite of an infected anopheline, screened houses, bed nets, and the prevention of mosquito breeding are the most important preventive measures. Native children and tramps often have latent malaria without symptoms, and hence proximity to them should be avoided. Several forms of quinin prophylaxis have been used, but the most statisfactory method is a daily dose of 0.4 to 0.8 gm., since the recipient suffers less from cinchonism than when larger doses are taken intermittently, and also he is more likely to remember to take the quinin. The size of the dose will, of course, vary with the form of the fever prevalent, as well as the degree of exposure. Treatment of pesrons who have had malaria and who, therefore, may act as sources of infection serves to protect the surrounding population.

Treatment.—Many years ago Osler said, "The physician who at this day cannot treat malarial fever successfully with quinin should abandon the practice of medicine." Craig in 1909 stated that, "The successful treatment of malaria by quinin depends wholly upon the proper administration of the drug. . . . I have yet to see a single case in which quinin, if given

early enough, did not succeed in curing the infection." During the past eight years the writer has not only followed the treatment of many cases, but has investigated, whenever possible, cases that were reported to be resistant to quinin. Not a single case has been found in which symptoms persisted even for three days after administration of as much as 30 grains of quinin daily. They may exist, nevertheless, but are certainly rare. The treatment of malaria, therefore, resolves itself into the proper use of quinin.

The best routine treatment for malaria (standard treatment) was recommended by the National Malaria Committee in 1918. The more nearly this is followed, except perhaps in very rare instances, the more successful will be the result:

> For the acute attack, 10 grains of quinin sulphate should be given by mouth three times a day for a period of at least three or four days. This should be followed by administration of 10 grains every night before retiring, for a period of eight weeks. For infected individuals without acute symptoms, only the latter part of treatment (administration of 10 grains nightly for eight weeks) is necessary.
>
> The doses for children are: age less than one year, ½ grain; one year, 1 grain; two years, 2 grains; three and four years, 3 grains; five, six, and seven years, 4 grains; eight, nine, and ten years, 6 grains; eleven, twelve, thirteen, and fourteen years, 8 grains; fifteen years and over, 10 grains.

While there may still be a difference of opinion as to just how quinin kills malarial parasites, or as to whether it acts as a direct or an indirect poison, there can be no doubt that it rapidly destroys them. Laveran observed in 1881 that a 1 : 1000 solution of quinin immediately stopped the amebic movement of the plasmodia, and Golgi noted that in preparations of the fresh blood of malarial patients who had been treated with quinin the parasites were shrunken and the protoplasm granular and opaque.

The first object of the treatment of malaria is to relieve symptoms by stopping the rapid reproduction of parasites. The quantity of quinin required to accomplish this varies very much in different individuals. Sometimes even as little as 5 grains daily is sufficient; while in other cases 10 or 20 grains or even more may be required; 30 grains always suffice and control the symptoms as quickly and as surely as larger doses. There is no means of determining in advance the minimum effective dose, and therefore it is always necessary to administer quantities which are known to relieve symptoms in all cases; 30 grains daily is about the minimum amount that can be absolutely relied upon.

The effect of quinin upon malarial parasites would no doubt be just as striking if the 30 grains were taken in a single dose, but since one large dose causes much more discomfort to the patient than several smaller doses taken at intervals, it seems wiser to administer 10 grains every eight hours. This usually prevents recurrence of the fever and chills after the first twenty-four hours and always controls symptoms within three days. Such large quantities of quinin need never be given for more than three or four days.

If patients are treated with quinin for three or four days only, a considerable proportion sooner or later suffer a relapse. This is a sign that all the parasites have not been killed and that infection has not been completely checked. As long as a single living parasite remains the patient is still infected and a relapse may occur at any time.

The parasites that remain after the acute symptoms have disappeared are lodged in the organs and tissues of the body, especially in the spleen and

bone-marrow; as they develop and reproduce they appear in the blood-stream. In order to destroy all of these there must be sufficient quinin in the blood at all times to kill them as soon as they enter the circulation; 10 grains a day is about the minimum quantity that will accomplish this. If this dose is taken daily, destruction of all the parasites is only a matter of time. The necessary duration of treatment varies in different individuals. Administration of 10 grains of quinin a day for a week prevents relapse in a few instances, but quinin therapy must continue for four weeks to cure 60 to 70 per cent. of cases; for six weeks to cure 80 per cent.; for eight weeks to cure 90 to 95 per cent.; and probably for twelve to fifteen weeks to assure cure in 100 per cent. of patients. There is no means of determining whether treatment must be brief or long, and whether or not cure is complete.

No salt of quinin is more effective than the sulphate. Capsules or tablets are as satisfactory as solutions and much less unpleasant to take. Quinin is more effective when given by mouth than when administered intravenously or intramuscularly. When given intravenously, however, its effect begins at once, whereas, after oral administration it does not act for one or two hours. Consequently in urgent cases of pernicious malaria one or more intravenous doses may save life. The bimuriate diluted with at least 20 c.c. of salt solution is a good preparation. The dose should never exceed 10 grains.

The treatment of hemoglobinuric fever is still debatable. There are strong advocates of treatment with quinin and just as strong opponents. It is certain that large doses of quinin increase hemolysis, and may, therefore, prove harmful. Consequently, only small amounts should be given until hemoglobinuria has ceased.

The general treatment of malaria consists of administration of a purgative at the beginning to empty the alimentary canal, rest in bed until the acute symptoms have subsided, and restriction to a liquid or light diet. The most satisfactory purgative is calomel (1 or 2 grains) followed by a saline.

Charles C. Bass.

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EPIDEMIC PLEURODYNIA

Definition.—Epidemic pleurodynia is an acute infectious disease characterized by the abrupt onset of a paroxysm of excruciating pleuritic pain, accompanied by fever and respiratory embarrassment, which lasts from four to twenty-four hours and tends to recur with lessened severity after intervals of one or two days of relative comfort.

History.—Patients have dubbed the condition "devil's grip," a term descriptive of the vice-like resistance to expansion of the chest caused by the pain during the seizure;

the term, however, is unfortunate, since it leads to confusion with the disease *la grippe*, to which it bears no relation.

The disease was described first by Dabney in 1888, when it occurred in epidemic form in Virginia. Since then it has appeared epidemically in Virginia in 1923, in New York in 1923, and in Pennsylvania and New Jersey in 1924.

Incidence.—So far as is known, epidemic pleurodynia has been confined to these areas. It has always appeared in summer and has been limited chiefly to urban communities and to seaside or mountain resorts. The epidemics die out quickly. The sexes are attacked with equal frequency, but children are more susceptible than adults.

Etiology.—A plasmodium which has been observed within the erythrocytes of patients during the acute illness is probably the specific etiological agent. Since this was discovered only in August, 1924, it has not been sufficiently confirmed. This organism, which was designated *Plasmodium pleurodyniæ* by Small in 1924, appears to be somewhat analogous to *Plasmodium malariæ*.

Nothing is definitely known of the mode of spread of the infection. The disease does not appear to be contagious. Greene's study of an institutional epidemic shows that water, milk, and foods do not carry the virus. The weight of evidence to date indicates that an insect probably spreads the infection through its bite.

Morbid Anatomy.—Epidemic pleurodynia has not proved fatal, so that no observations of its pathological anatomy have been made. The symptoms suggest involvement of the diaphragm, but the transient character of the pain is incompatible with the usual course of inflammatory processes. Again, the symptoms may be considered as the result of an intercostal neuritis, but this conception leaves unexplained the special regional selectivity of the causative neurotropic irritant.

Symptoms.—The *period of incubation* is from two to five days. The patient feels well throughout this interval. The *attack* always begins suddenly with pain as the initial symptom, accompanied by a rapid rise of temperature, an increase in the pulse rate, and also in the frequency of respirations, which become shallow and painful. Headache occurs rather constantly, backache occasionally, and pain in the extremities rarely. Infrequently a chill, or chilly sensations, immediately precedes the onset of pain. The temperature reaches its maximum (101°–104° F.) within several hours after the onset of the pain; the rise is accompanied by the phenomena associated with acute fever—loss of appetite, coating of the tongue, slight delirium, and concentration of the urine. Pain is the outstanding symptom. It is lancinating in character, and located over the attachments of the diaphragm to the anterior thoracic wall on either the right or the left side, or at times in the epigastrium. It may be referred downward over the abdominal wall. The pain is greatly aggravated by the respiratory movements, and by any movement of the body, especially by extension of the trunk. It subsides with the recession of fever, and may shift from the initial site to the opposite side with subsequent paroxysms. Tenderness over the painful regions is common, and may lead to slight abdominal rigidity in certain instances.

The skin is hot, dry, and flushed during the height of the fever, but with the decline of temperature sweating occurs usually within less than twenty-four hours after the onset. The patient is at this stage free from pain and sinks into refreshing sleep.

Aside from the increase in the heart rate (90–120 beats per minute) no abnormalities are found in the circulatory system. The lungs reveal no pathological changes, and the Roentgen ray fails to demonstrate any intrathoracic lesions at any time during the illness. The respiratory rate may reach 30 to 45, or even 60 per minute. The inspirations are shallow, and a slight cyanosis may be noted at the height of the respiratory embarrassment. The gastro-intestinal symptoms are not prominent. Slight anorexia accompanies the fever. Nausea and vomiting may occur, but these are never troublesome. A tendency to constipation usually precedes and accompanies the paroxysm. During convalescence diarrhea has been occasionally noted. Neither the liver nor the spleen is enlarged.

The disease may terminate with a single paroxysm, or after an interval of one or two days of comfort the attack may be repeated, but usually in milder form than at first. The second paroxysm frequently begins at about the same hour of the day as did the first. More than two are infrequent.

Laboratory studies of the blood fail to show bacteria in cultures, do not reveal a leukocytosis, and except for the demonstration of the plasmodium have been almost entirely negative. Occasionally a stippled erythrocyte is observed.

The disease does not lead to great prostration. *Convalescence* is rapid. Complications and sequelæ are rare. No deaths have resulted.

Diagnosis.—The suddenness of onset, the seat and character of the pain, the short duration of the fever, the tendency to recurring paroxysms on the third or fourth day, and the speedy and uncomplicated recovery constitute a clinical picture which should rarely be confused with other conditions. The onset differs from that of *pneumonia* by the absence of cough and of physical signs within the chest, by the transient character of the symptoms, and by the absence of leukocytosis. There are no physical signs to suggest *acute pleuritis*. Tenderness and slight rigidity of the abdominal muscles may lead to confusion with *acute intra-abdominal surgical conditions*. This rigidity is easily overcome in epidemic pleurodynia, since there is no deep tenderness and peristalsis is not affected. From *dengue* it is differentiated by the absence of "break-bone pains" and of a skin rash. *Acute gastro-intestinal upsets* consistently cause more troublesome vomiting and diarrhea than does this condition. *Malaria* is differentiated by the microscopical findings in the blood.

Treatment.—Absolute rest in bed is the first requisite for the comfort of the patient. The pain may be so severe as to require morphin, but usually the salicylates and antipyrin suffice. The prompt exhibition of quinin in doses of 3 to 5 grains (0.2–0.33 gm.) every two hours until 20 to 30 grains (1.33–2 gm.) have been given appears to terminate the disease, specifically, and to prevent the recurrence of paroxysms. Half of this daily dosage should be maintained for a period of one week after the temperature has become normal.

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TRYPANOSOMIASIS

AFRICAN TRYPANOSOMIASIS

(*Sleeping Sickness*)

At least two distinct varieties of trypanosomiasis are known in Africa—Gambian and Rhodesian sleeping sickness. Both are limited to tropical Africa. The Gambian type is irregularly distributed over an enormous area, and, because of the habits of its insect vector, *Glossina palpalis*, follows water-courses. It is found on the west coast from Senegal southward to Angola, and extends eastward from Bahr el Ghazal, Lake Albert, and Lake Victoria on the north to Lake Banguelo in the south. The Rhodesian type is limited to a much smaller area, occurring only in portions of Nyasaland, Rhodesia, and German and Portuguese East Africa.

Gambian Sleeping Sickness.—The Gambian disease is caused by *Trypanosoma gambiense*. For a description of this parasite, as well as of trypanosomes in general, the reader is referred to standard works on protozoölogy. Suffice it to say here, that *Trypanosoma gambiense* is a typical polymorphic mammalian trypanosome, which varies in length from 10 to 39 micra and possesses a spindle-shaped body which moves sinuously because of its undulating membrane and free flagellum. It reproduces by longitudinal fission and, so far as is definitely known, retains its trypaniform structure throughout its life-cycle in man. Transmission from man to man is effected by the tsetse fly, *Glossina palpalis*. After the fly has become infected by ingesting blood from an infected human being the parasites undergo a definite developmental cycle which lasts twenty days or more. Eventually they invade the salivary glands, where, once established, they constitute a constant source of infection when the fly bites uninfected persons. Occasionally transmission may take place mechanically by means of *Glossina* or other biting insects, or by coitus.

Much evidence indicates that the trypanosomes occur not only in man but also in a great number of the wild animals, which, therefore, acting as reservoirs maintain the infection in *Glossina* and form a well-nigh insurmountable obstacle to the eradication of the disease.

In man the trypanosomes are found chiefly in the blood-vessels and lymphatics. They may, however, invade the connective tissues and the substance of the various organs, a fact which may, indeed, account for the tissue lesions.

The length of the incubation period has not been accurately ascertained, but is probably much shorter than was originally supposed. Initial symptoms have appeared in some cases fourteen days after inoculation. The disease itself generally passes through two stages, the first being sometimes known as the *trypanosome fever stage*, and the second as the *sleeping sickness stage*. "The first is characterized principally by irregular attacks of fever, chronic polyadenitis, exanthemata, frequency of the pulse and respiration, and asthenia; the second, by exaggeration of the symptoms of the first stage, marked emaciation, and by the appearance of nervous symptoms, tremors, incoördination of movements, paralyses, mental disturbances, apathy, somnolence, coma, and death. These two stages are, as a rule, not clearly delimited, but merge into one another, the second stage gradually manifesting itself as the nervous symptoms develop following injury to the

nervous tissue from the inflammatory changes in the lymphatics of the brain and spinal cord." (Blacklock and Yorke).

Rhodesian sleeping sickness is caused by *Trypanosoma rhodesiense.* In the human host, the morphology of the species is identical with that of *Trypanosoma gambiense.* In subinoculated animals, however, the nuclei of some of the short forms (not over 5 to 6 per cent.) migrate posteriorly to the parabasal body to form what are known as posteriorly nucleated forms. The course of the disease is similar to that of the Gambian type, except that *Trypanosoma rhodesiense* is much more virulent for man and is much more resistant to treatment. *Trypanosoma rhodesiense* is transmitted by *Glossina morsitans.* In this insect its development is similar to that of *Trypanosoma gambiense* in *Glossina palpalis,* with the exception that it may be completed within fourteen days after ingestion of the infected material.

Diagnosis.—Although certain clinical symptoms arouse suspicion, definite diagnosis can be made only by demonstration of the parasites. This is often difficult because of the scarcity of the parasites in the blood. No reliable serological tests have been devised and cultivation *in vitro* is too difficult to be of any service.

Microscopical examination of the blood may be made either with a drop of fresh blood under a cover-slip or with a stained smear. The former method is preferable because the characteristic agitation of the blood-cells by the living trypanosomes facilitates their detection. If auto-agglutination of the red cells is observed, further search is always advisable. In suspected cases when none of the organisms can be discovered it is best to examine a large quantity of blood; 10 c.c. may be withdrawn from a vein, citrated or oxalated, and then centrifuged at low speed to throw down the red cells. The supernatant fluid is then withdrawn and recentrifuged at high speed. The sediment should be examined for parasites. Often by this method the trypanosomes may be discovered, even though they are extremely scarce in the blood.

Gland Puncture.—When the glands (particularly those of the posterior triangle of the neck) are enlarged and soft their tissue fluid almost invariably contains trypanosomes. A small quantity of this may be sucked out with a sterile, dry hypodermic needle. In old or treated cases, where the glands are often sclerosed, this method, of course, is unsuccessful.

Lumbar puncture is of value in the second stage of nervous involvement because the sediment from centrifuged spinal fluid often contains trypanosomes. Since the cell content of the spinal fluid increases with cerebrospinal involvement, the cell count may furnish a rough index of the extent of cerebrospinal invasion.

Inoculation Into Susceptible Animals.—Laboratory animals, such as rats, mice, guinea-pigs, rabbits, and monkeys, may be inoculated subcutaneously or intraperitoneally with suspected blood, fluid from the gland, or spinal fluid, and their blood examined for trypanosomes.

Trypanosoma gambiense and *Trypanosoma rhodesiense* can be differentiated by the posteriorly nucleated forms which develop in subinoculations of the Rhodesian strain. In lieu of this, the characteristics of geographical distribution, virulence, and resistance to chemotherapeutic agents are of value.

Treatment of sleeping sickness after the beginning of the second stage is practically useless, but treatment in the early stages results in the pro-

longation of life and in the definite cure of a certain proportion of patients. The prognosis for the Gambian type is much better than for the more virulent Rhodesian type.

Among the various organic arsenicals, atoxyl, which was first introduced by Thomas in 1905, is still considered one of the most efficient drugs. Adults can tolerate doses of 0.5 to 1 gm., but on account of the visual disturbances which it produces smaller doses are preferable. Intramuscular or subcutaneous injections of a 10 per cent. solution should be given first at intervals of five or six days, then at longer intervals; the treatment should be continued for long periods. Plimmer and Thompson in 1907 first pointed out the efficiency of tartar emetic (sodium or potassium antimonyl tartrate) in experimental trypanosomiasis. This can be given in doses of 0.5 to 1 gm., two or three times a week for long periods. It is best given in a 1 per cent. solution intravenously. Even a minute quantity of the drug given subcutaneously or leaking into the tissues around the vein produces intense pain. Another useful antimonial is antimony trioxid, which can be injected intramuscularly in the form of *injectio antimonii oxidi* (Martindale).

Since the *Trypanosoma rhodesiense* is particularly resistant to arsenicals, the use of antimony is especially desirable in Rhodesian sleeping sickness; and it is very probable that a combination of arsenicals and antimonial treatment is advantageous in the treatment of both diseases.

Among the recent advances in the treatment of trypanosomiasis the most notable are the results obtained (1) with *tryparsamid* (the sodium salt of *N*-phenylglycineamid-*p*-arsenic acid), which was first synthesized and studied at the Rockefeller Institute for Medical Research, and (2) with *Bayer 205*, a proprietary drug, the composition of which has not been divulged and which is manufactured in Germany. These substances bid fair to revolutionize the treatment of the disease.

SOUTH AMERICAN TRYPANOSOMIASIS

(*Chagas' Disease*)

South American trypanosomiasis, or Chagas' disease, is found chiefly in Brazil, but has occurred in San Salvador, Venezuela and Peru, and may be widely distributed over South America.

The causative agent, *Trypanosoma cruzi*, when found in the blood, has an ordinary trypaniform structure and averages about 20 micra in length. The parasites, however, unlike those of the African disease, do not reproduce in the blood, but invade the tissues and are transformed into typical leishmania-like parasites. These tissue or leishmaniform bodies are spherical, vary from 2 to 4 micra in diameter, and exhibit the same structure as the Leishman-Donovan bodies found in kala-azar or oriental sore. They may be again transformed into trypaniform bodies and re-enter the blood. The infection is transmitted from man to man by several species of reduviid bugs, chiefly *Triatoma megista*. The bug receives its infection by ingesting infected blood, but whether man is infected by the bite of infected bugs or from the feces of such bugs is not definitely known.

The disease can generally be divided into two stages—acute and chronic. The *acute stage* generally lasts twenty to thirty days, and is characterized, especially in children, by fever, myxedematous swellings, and enlargements of the thyroid and lymphatic glands, liver, and spleen. During this stage

the trypaniform parasites are present in the blood and the leishmaniform bodies are found in the tissues. If the patient survives this stage the disease becomes chronic and may persist for many years. During the *chronic stage* the trypaniform parasites disappear from the blood, but the tissue infection with the leishmaniform organisms continues. Symptomatically this stage is characterized by the occurrence of various organic syndromes, the character of which depends upon the systems and organs chiefly involved. Considerable doubt exists as to whether all of the symptoms described by Chagas are actually due to *Trypanosoma cruzi* or to superimposed infections.

Diagnosis.—As diagnosis can be made definite only by finding the parasites, it is seldom possible except during the acute stage, when the trypaniform organisms are still in the blood and when their presence can be demonstrated by microscopical examination or injection into susceptible laboratory animals. Gland puncture has not yielded any results in this infection, but in some cases when there was cerebrospinal involvement the parasites have been found after lumbar puncture. Attempts to recover the leishmania stages by puncture of the various muscles and organs have not been successful.

Treatment.—So far none of the usual trypanocidal drugs have been found to be of any value in the treatment of infections with *Trypanosoma cruzi*.

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KALA-AZAR

(Leishmaniasis, Dumdum Fever, Non-malarial Remittent Fever, Cachectic Fever, Black Fever)

Definition.— Kala-azar is an infectious disease characterized by enlargement of the spleen, anemia, and leukopenia. It is caused by a protozoan, *Leishmania donovani*.

History.—A disease, erroneously called "malarial cachexia," was described by Clarke in 1882 from Assam, India. An epidemic of this disease spread up the Brahmaputra Valley from 1875 to 1903, and in some districts caused the death of more than half the population. Sporadic cases with similar symptoms have been observed in the Greek islands and in Italy. In 1903 Leishman described the parasite found at the autopsy of a British soldier invalided from Dumdum, near Calcutta. Soon afterward Donovan recovered the same organism from the spleen of a living patient in Madras. From this material Ronald Ross named the organism *Leishmania donovani*. In 1903 Marchand described the "cell inclusions" in the organs of a German soldier sent home from Tsingtao, Shantung Province, China, which, with Ledingham, he later identified as Leishman-Donovan bodies.

Incidence.—Kala-azar has been found in all the countries of the Mediterranean littoral, the Sudan, West Africa, Mesopotamia, Southern Russia, Russian Turkestan, Northeast India, Madras, Sumatra, and North China. It most commonly affects individuals in the first and second decades of life, but may occur in patients even seventy or more years old. There is no difference in sex incidence. The disease is far more common in the country than in cities. In India and China, at least, kala-azar is confined to alluvial plains or low hills with an altitude of less than 2000 feet.

Etiology.—The fact that in cultures and in some insects *Leishmania donovani* grows into a flagellate resembling the common insect herpetomonads, suggests that an insect is an essential host. Basile attempted to prove the transmission of the so-called infantile form from the dog by means of the dog flea (*Ctenocephalus canis*). Patton has demonstrated the development of Leishmania in the Indian bedbug (*Cimex rotundatus*), but has not succeeded in transmitting the disease by means of this insect. The question of transmission is, as yet, unsolved. French and Italian investigators have considered the canine and human diseases identical, but this is not proved. Kala-azar of dogs is unknown in India and China.

Protozoölogy.—*Leishmania donovani* belongs to the Mastigophora (Flagellata). It is found in man as an oval, non-flagellate organism 1.5 to 3 x 2 to 4 micra, the so-called Leishman-Donovan body. It contains two chromatic masses: the nucleus (macronucleus, trophonucleus), which is the larger, is nearly round and is usually applied to one of the flatter sides of the cell; the blepharoplast (micronucleus, kinetonucleus), the smaller, is usually rod shaped and most frequently lies with its long axis at or nearly at right angles to the nucleus. Giemsa's stain renders the nucleus lilac to magenta in color, the blepharoplast purple, and the cytoplasm sky blue or unstained. Leishmania is most easily cultivated on the Novy-McNeal-Nicolle (N. N. N.) medium at 22° C. Cultures usually die when contaminated by bacteria.

Pathogenesis.—Hamsters, white mice, monkeys, and dogs can be artificially infected with this organism. Some of these species tend to recover spontaneously from the infection. Rabbits and guinea-pigs are resistant.

Morbid Anatomy.—Kala-azar (generalized, systemic, or visceral human leishmaniasis) is essentially an invasion of the endothelial cells of the body by *Leishmania donovani*. The parasites are taken up by the endothelial cells in which they multiply until the cells burst and set them free in the circulating blood. Hence they are again taken up by other similar cells in which this process is repeated, or by polymorphonuclear leukocytes. Wandering endothelial cells also thus protect and distribute the parasite. The polymorphonuclear leukocytes probably destroy them, at least under certain favorable conditions. The organism is found in largest numbers in

organs where the phagocytic endothelial cells are most numerous, *i. e.*, in the spleen, liver, bone-marrow, and lymph-nodes. They are less abundant in the endothelial lining of the small and medium-sized vessels throughout the body, and especially in granulation tissue.

At autopsy the body is usually pale and emaciated. Pigmentation may be increased. The skin is dry and rough. The *heart*, exceptionally, contains tiny nodules composed of small round cells and parasitized endothelial cells. The *lungs* show nothing characteristic, but are frequently the site of acute complications. The *spleen* may be enlarged ten to fifteen times. Its consistency varies from soft to rather hard, according to the stage of the disease, the treatment, and the complication from which the patient dies. The capsule is smooth except for occasional patches of perisplenitis over infarcts. On section, the purple to reddish-brown pulp bulges from the capsule. The trabeculæ and Malpighian corpuscles are usually not prominent because the quantity of pulp is increased. Microscopically a great increment in the reticular epithelium is demonstrable, the cells containing Leishman-Donovan bodies, sometimes in enormous numbers. The organ is usually greatly congested. The *liver* is enlarged and frequently mottled with yellow—the nutmeg liver of fatty degeneration. Microscopically the fatty degeneration is most marked in the central zone of the lobules, where numerous Kupfer's cells, either free or attached to the walls, almost block the lumen of the capillaries. In some cases the interlobular tissue contains parasitized endothelial cells. These may be associated with the lymphatics. Exceptionally Leishmaniæ are present in the liver cells in small numbers. The *lymph-nodes* are sometimes enlarged and contain the characteristic cells in the lymph spaces. The *red marrow* is usually so increased as to entirely replace the yellow marrow of the long bones; it contains parasitized cells sometimes in larger numbers than the spleen and liver. The *intestines* are frequently the seat of ulcers, which result from complications rather than from the disease itself. In the granulating walls of these lesions Leishman-Donovan bodies can sometimes be found. In the *kidneys* only rarely are there parasites; recently, however, Shortt has cultivated Leishmania from the urine. Occasionally organisms are found in cells of the loose connective tissue of the *tunica vasculosa* and *septula testis* of the *testicles*. Being essentially associated with vascular endothelium, they may be found in any organ of the body, but only exceptionally and in small numbers. In granulation tissue, regardless of situation, they are not uncommon.

Symptoms and Physical Signs.—Nothing is known definitely of the *incubation period* of the disease. Experimental animals (hamsters) show visceral infection four days after intraperitoneal inoculation. The *onset* is *insidious* in most cases, and the patient can remember no definite beginning of symptoms, but only indefinite attacks of fever. Physicians not infrequently fail to recognize the condition, especially in the early stages. A *typhoid-like* onset is not uncommon. The patient becomes ill, within a few days developing a high continuous or remittent fever (temperature 103° to 104° F.). The spleen is slightly enlarged. Usually there are no intestinal symptoms. Unlike typhoid fever, kala-azar makes the pulse rapid. There may be a remission of the fever after a few weeks or, in the various types noted later, it may continue. A *malaria-like* onset is also frequent. Many patients state that an attack of malaria marked the beginning of the disease, but on careful questioning it appears that the so-called "chills"

were merely chilly sensations and not rigors, and that there was neither sweating nor definite periodicity of the attacks.

Whatever the form of onset, the temperature rises to 103° to 105° F. Rogers first noted the occurrence of a double remittent type of pyrexia, *i. e.*, a rise and remission twice in twenty-four hours. This type of fever is by no means pathognomonic, although it is very suggestive of kala-azar. In order to demonstrate its occurrence the temperature should be taken every two hours. Occasionally three daily rises and falls are seen. If not of this peculiar form, the fever may be of many types—high or low, continuous, remittent or intermittent, and associated with comparatively afebrile periods. It may be necessary to determine the temperature at intervals throughout the night to demonstrate a rise. Other symptoms frequently encountered are headache, weakness, and cough.

Functional cardiac murmurs caused by the anemia are to be heard in most well-established cases. *Hemorrhages*, especially from the nose and gums, are common. *Edema* of the feet and *ascites* are not rare when the disease is advanced.

Blood Changes.—Kala-azar is characterized by anemia, leukopenia, a diminution in the number of blood-platelets, and an increase in the serum globulin content of the blood. The *anemia* is secondary. The red cell count averages about 3,000,000 per cubic millimeter, the hemoglobin content, 60 per cent. Nucleated erythrocytes are not uncommon, especially in children. The number of reticulated cells is slightly in excess of normal. The *leukopenia* is due to an absolute decrease in the quantity of cells of myelogenous origin, *i. e.*, the granular leukocytes. If there is a concomitant helminth infection the eosinophil count may be normal or high. Rogers has pointed out that the leukopenia is often more serious than the anemia, less than 1 leukocyte per 1000 erythrocytes being present. In advanced cases, especially when there are hemorrhages, the *bleeding time* is prolonged and the number of *platelets* decreased. Bramachari first called attention to the precipitate which forms when serum from patients with kala-azar is diluted with distilled water, and Sia and Wu have shown that this is due to a marked increase in the serum globulin content.

Physical Examination.—Patients with advanced kala-azar are weak and emaciated. The skin is rough, the hair dry and thin. Dermal pigmentation may be increased, but this is not a constant feature of the disease. The conjunctivæ, finger- and toe-nails, palms, and soles are pale. The carotids pulsate markedly and the cardiac impulse is noticeable against the thin chest wall. In early, though thoroughly established cases, there may be no signs other than a persistent, irregular fever, a moderate anemia, and a slight enlargement of the spleen. Innumerable gradations between these two conditions occur. In very early stages, palpation of the *spleen* is difficult; usually, however, it is several centimeters below the costal margin when the patient presents himself for treatment. The consistency is much less hard than in chronic malaria. In kala-azar the spleen softens perceptibly under treatment, sometimes during a complication and sometimes for no apparent reason. It is usually not tender. Ordinarily the *liver* is also definitely enlarged and its edge palpable and sharp.

Complications are frequent and are more apt to cause death than the disease itself. *Cancrum oris* is perhaps the most frequent, characteristic, and serious. It begins as a slight ulceration on the buccal mucosa or, less

frequently, on the hard or soft palate. This spreads in spite of treatment and is usually fatal. *Acute respiratory infections* are also very common. *Bronchopneumonia* is one of the most frequent causes of death. The antimony used to combat kala-azar acts as a bronchial irritant. *Dysentery* has been considered by some a symptom of the disease rather than a complication, but usually the presence of the amebæ or bacilli of dysentery can be demonstrated by suitable laboratory tests. *Diarrhea* is not infrequent. Sometimes intestinal flagellates are found in such stools. The *exanthemata* and other *infectious fevers* are easily contracted by subjects of kala-azar and frequently terminate fatally.

Diagnosis.—For absolutely certain diagnosis the etiological agent must be found in smears or cultures.

Spleen puncture, which permits examination of the splenic juice for the organisms, may be undertaken without great risk if the bleeding time is not more than five minutes (normal three minutes).

A sterile syringe and needle (No. 22 or 24) which are dry or rinsed with sterile saline or citrated Locke's solution should be employed. The skin over the most prominent part of the enlarged spleen must be sterilized with iodin and alcohol and the site of puncture preferably anesthetized with novocain or some similar drug. The spleen is steadied by an assistant. The patient is cautioned to hold his breath. The needle is thrust nearly vertically into the spleen to a depth of about 3 cm. and gentle suction exerted while it is slowly withdrawn. Before the point of the needle reaches the surface of the spleen the piston should be released. After smears (like blood-smears) have been made with the spleen juice, Giemsa's stain or any other good modification of the Romanowsky stain may be applied. The organisms appear in the large mononuclear endothelial cells, or extracellularly if the cells have been ruptured in making the smear.

Liver puncture has been advocated as safer, but provides much less chance of finding the organisms.

Smears of peripheral blood usually contain so few organisms that many must be examined. The organisms are usually in the polymorphonuclear leukocytes along the edges or in the tail of the smear. By special technic with larger quantities of blood they usually can be demonstrated in untreated cases.

Spleen cultures may be made on N. N. N. medium from the material obtained at spleen puncture by observing the strictest asepsis and incubating at 22° C. The flagellate forms appear after from five to twenty days.

Blood-cultures may be made directly from a few drops of blood or, preferably, by special technic with larger quantities.

Presumptive Tests.—The *globulin precipitation phenomenon* occurs in schistosomiasis as well as kala-azar, but is nevertheless of great diagnostic value. In this test, to a small test-tube containing 0.6 c.c. of distilled water, 0.02 c.c. of blood from the ear or finger-tip is added by means of a Sahli hemoglobinometer blood pipet, mixed, and allowed to stand. A flocculent precipitate appears and begins to fall, in well-marked cases, within five minutes; in mild cases, more slowly. Leukemic blood gives a false test because of the undissolved nuclei of the leukocytes. A drop of dilute acetic acid dissolves the globulin, but not the cell nuclei.

The *aldehyd* or *formol-gel* test of Napier is made by adding a drop of formalin to about 1 c.c. of blood-serum from the patient. In positive cases the serum becomes opaque and solidifies as though coagulated by heat, usually within a few minutes. Opacity alone or solidification alone are of doubtful significance.

Differential Diagnosis.—*Chronic malaria* renders the spleen harder and less enlarged than advanced kala-azar, causes the appearance of plasmodia in the blood, does not produce globulin precipitation, and is usually evidenced by definitely periodic chills and sweating which yield to quinin. Rarely both diseases may occur together.

Early kala-azar is frequently mistaken for *typhoid fever*, but the latter disease and the *paratyphoid fevers* are of shorter duration and are distinguished by specific agglutination tests, and frequently by blood and fecal cultures. The size of the spleen is of no diagnostic assistance early in the disease, but later aids differentiation because it is larger and harder in late kala-azar.

Banti's disease does not cause a relative decrease in the number of granular leukocytes. The globulin precipitation test is negative. The final differentiation, however, depends upon the presence or absence of Leishmania.

Intestinal schistosomiasis produces very great enlargement of the liver, followed by hepatic cirrhosis with ascites. Eggs of the blood-fluke are present in the stools.

Syphilitic splenomegaly is recognized by the positive Wassermann reaction and the response to specific treatment. It does not render the globulin test positive.

Febrile infantile splenic anemia, which Nicolle reported from North Africa, is differentiated from kala-azar by the age incidence and the greater hardness of the spleen. It occurs in infants less than six months old. Leishmaniæ are not obtained on spleen puncture. The patients usually recover spontaneously.

Prognosis.—Without treatment most subjects of kala-azar die within four months to two years, usually as the result of *cancrum oris*, pneumonia, or dysentery, but often from other infectious diseases. Occasionally those who survive *cancrum oris* or pneumonia are cured of the primary disease or have a marked remission.

Treatment.—Antimony is a specific for the leishmaniases. It was first applied to the treatment of the South American mucocutaneous disease by Vianna and Machado, and to kala-azar by Di Cristina and Caronia. Although in different hospitals there are slight variations in technic, the following procedure employed at the kala-azar clinic of the Peking Union Medical College Hospital may be taken as a fair example: A 2 per cent. solution of sodium antimony tartrate, prepared with fresh, double-distilled water, is sterilized in the autoclave. Intravenous injections are given thrice weekly according to the schedule shown on page 386. Or 2 mgm. of the salt per kilo of body weight may be considered the average tolerated dose. One-half of this should be given at the first injection, three-quarters at the second, and the full quantity at the third or fourth. Thereafter, after every three or four injections, the dose should be cautiously increased to the limit of tolerance.

The increase in dose must be gaged by the reaction of the patient. *Early reaction:* (*a*) soon after injection: dizziness, coughing, and vomiting; (*b*) some hours after injection: pain in the extremities (joints and muscles) and fever. If the reaction be slight, the following dose is not increased; if severe, it is reduced or omitted. If possible it is best to administer doses up to the limit of tolerance. *Late reaction* or *cumulative effect:* (*a*) bronchitis and even

Time.	Dose for—		
	Adults, c.c.	Children—	
		10–15 years, c.c.	Under 10 years, c.c.
1st week (1)	1.5	1.0	0.5
(2)	2.0	1.0	0.5
(3)	2.5	1.5	1.0
2d week (1)	3.0	1.5	1.0
(2)	3.0	2.0	1.5
(3)	3.0	2.0	1.5
3d week	3.5	2.5	2.0
4th week	4.0	3.0	2.5
5th week	4.5	3.0	2.5
6th week	4.5	3.5	2.8
7th week	5.0	3.5	2.8
8th week (1), (2), (3)	5.0	3.8	3.0
9th week	5.5	3.8	3.0
10th week	5.5	3.8	3.0
11th week	6.0	4.0	3.3
12th week	6.0	4.0	3.3

bronchopneumonia result from the effect of antimony on the respiratory mucosa, and (*b*) the drug also causes renal irritation and the appearance of albumin and casts in the urine. The urine should, therefore, be examined frequently, especially in the early part of treatment. If symptoms of irritation develop, the antimony should not be given until the patient becomes normal.

Some physicians advocate a month's interval after three months' treatment (forty injections), and, if necessary, a second course of therapy with doses somewhat smaller than those given at the end of the first course. Others prefer to administer a 1 per cent. solution of the sodium salt or the tartar emetic (potassium antimony tartrate) which was first used in kala-azar therapy. Rogers advocated the use of colloidal antimony sulphid, but this gives no better results than the simpler preparations.

The best site for intravenous injections is the bend of the elbow, but in children it may be necessary to puncture the jugular vein. Care must be taken to avoid injecting the solution into the perivascular tissue, for severe pain ensues and a brawny induration which makes subsequent injection difficult or impossible. As an auxiliary treatment in refractory cases Muir advocates the injection of a turpentine, camphor, creosote, and olive oil mixture into the *gluteus* or *latissimus dorsi* muscle. This treatment has not, however, gained wide acceptance. A safer and more rational measure is blood transfusion, which reduces the bleeding time and often gives the patient a start toward recovery when intravenous administration of antimony alone is insufficient.

The effect of the antimony treatment is often not apparent until after ten to fifteen injections. The patient then begins to show less lassitude, less fever, has a better color, a smaller spleen, and a diminishing globulin reaction. With the first improvement patients are likely to consider themselves cured and discontinue treatment, and it is consequently essential to explain at the beginning the necessary length of the course of injections if cure is to be lasting. Practically all who persist are cured unless they succumb to

complications. Patients should be inspected at intervals for a year after the treatment has been completed.

Treatment of Complications.—*Cancrum oris.*—After the slough of *cancrum oris* has been removed, 50 per cent. silver nitrate solution should be applied daily. When granulation has begun, it is advisable to use a 10 per cent. solution twice a day. Salvarsan is advocated by some, but others consider it dangerous because of the liver lesion always present.

The treatment of other complications is in nowise different from the measures employed when they are encountered as primary diseases.

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RELAPSING FEVER

(Febris Recurrens, Ruckfallfieber, Spirillum Fever, Tick Fever)

Definition.—Relapsing fever is an acute infectious disease characterized by recurrent attacks of fever which are usually separated by afebrile and otherwise symptomless intervals. The course of this disease is remarkable in that the onset is usually stormy, the attacks generally short, and their terminations wholly unexpected. It is caused by several varieties of spirochetes which are transmitted to man from ticks and lice.

History.—The first references to relapsing fever date back to 1741, when Rutty observed a disease of this type associated with typhus fever in Dublin, and to 1857, when Livingston reported that in South Africa a peculiar relapsing fever often followed the bite of a tick. Obermeyer's observation in 1868 that a large spirillum was present in the blood of a patient was confirmed in a German epidemic in 1872, when he was able to find this organism in the blood of a large number of patients. His discovery was not, however, published until the following year. That African tick fever is caused by a spirochete was not proved until 1904 and 1905.

Incidence.—*Louse-borne relapsing fever* is endemic, but at times becomes epidemic in European Russia, Poland, and the Balkan States. These re-

gions have constituted the chief centers of distribution of the disease in Europe for about two centuries. Sporadic cases and mild epidemics occur from time to time in China, India, and North and West Africa. During the World War there were more than 12,000 cases in Serbia, and in 1922 and 1923 about 600 people of the Gold Colony in West Africa are reported to have had relapsing fever.

During the seventeenth and eighteenth centuries several epidemics occurred in Ireland, Scotland, Austria-Hungary, Germany, and Russia. The disease is now rare in England, Ireland, and Scotland. During 1869, however, importation of relapsing fever from Ireland to New York and Philadelphia produced several small epidemics in the United States. These, fortunately, did not spread, and the disease is not endemic in this country.

The chief center of African relapsing fever which is transmitted by *ticks* is probably to be found in German East Africa, whence it spreads along the main caravan routes. The incidence is relatively high in Uganda, the Congo Free States, British Central Africa, and Portuguese West Africa; and this type of relapsing fever is endemic in Palestine, Persia, and parts of Central and South America. It also occurs sporadically in Southern California and Mexico.

Epidemic relapsing fever and typhus fever are frequently associated, and are both apt to occur in the periods of depression which often follow war, famine, and social upheavels. The overcrowding, lack of personal hygiene, and inevitable dissemination of vermin common at such times permit the development of serious epidemics from endemic foci. The tick-borne fever does not often become epidemic, for the natives who are continuously exposed are immune, and very few Europeans ever chance to sleep in the tick-infested native houses or along the caravan routes.

Etiology.—Relapsing fever is caused by a spirochete of the genus *Spironema*, to which different names have been given in different parts of the world. On the basis of immunological studies, variation in clinical pictures, and differences in vectors, the following "species" have been described:

Spironema berbera.....of Algeria and possibly Egypt.
Spironema recurrentis.....of Europe—North and West Africa.
Spironema duttoni.....of South and Central Africa.
Spironema novyi.....of North America.
Spironema carteri.....of Asia.
Spironema neotropicalis.....of Panama.

Morphologically, the relapsing-fever spirochetes show no constant differences, hence a description of one suffices for all.

Spironema recurrentis (Lebert, 1874) has an average length of between 18 and 23 micra; a breadth of about 0.3 micron, and usually contains three to six turns which are generally considered to be flexible. In fresh coverslip preparations from infected blood they may be seen to move backward and forward for a distance of about twice their length. The movement is in two directions, one of progression and one of gyration, about the line of progress. Multiplication is by transverse fission.

Noguchi and others have succeeded in cultivating the spirochete of relapsing fever on artificial media. Ordinarily, neutral ascitic fluid, containing a sterile piece of rabbit kidney and a few drops of blood, or a medium composed of rabbit serum, normal salt solution, and 0.1 per cent. neutral

agar or 1 per cent. peptone, will be found satisfactory. Cultivation, however, is not a practical diagnostic procedure.

Life Cycle of Spironema.—(*a*) *In the Vertebrate Host.*—The spirochetes appear in the peripheral blood of man, monkey, and certain rodents in about one week after their entrance into the tissues. Rapidly dividing in the blood, they sometimes become more numerous than the red blood-cells. Following this stage in their development, which lasts several days, the parasites suddenly disappear almost completely from the peripheral circulation. For a period of about one week following their disappearance it is unusual to find a single spirochete by direct examination of the blood. This latter condition is ended by a reappearance of spirochetes and the beginning of a second period of rapid multiplication. Ordinarily their maximum number is now far less than that observed in their initial appearance and their stay in the blood is usually curtailed. This sequence of appearance, multiplication, and disappearance may take place several times, but ordinarily after one or two cycles of development the spirochetes are destroyed by the antibodies in the blood of the host.

(*b*) *In the Invertebrate Host.*—There is evidence of a cyclic development of the relapsing-fever spirochete in the tissues of lice and ticks somewhat comparable to that observed in man. Leishman, supported by experimental evidence of his own and of others, believes that in the tick the spirochetes undergo a metamorphosis into granules. These granules are said to be taken up by the cells of the tick and under favorable conditions develop into spirochetes.

Mode of Transmission.—Relapsing-fever spirochetes are not transferred by the bite of the louse. They are liberated upon an accidental crushing of the infected lice by their host. They find easy access to the body through the abrasions caused by scratching. Transmission by the tick is also indirect. During the course of a meal of blood the tick secretes a clear fluid, which bathes the under surface of its body, and conveys the infected excrement of the tick to the wound of the bite.

Biting flies and mosquitoes, as well as the bedbug, may mechanically convey the infection; that is, upon being interrupted during their feeding on a relapsing-fever subject and allowed to complete their meal on a normal, there may result a mechanical transfer of the spirochete from the sick to the well.

The Vectors.—*Lice* (*Pediculus vestimenti* and *Pediculus capitis*, de Geer, 1778).

Incrimination of the louse as a carrier of relapsing fever was first advanced by Flugge in 1891. Mackie (1907), as a result of an epidemiological survey of an epidemic in India, concluded that *Pediculus corporis* was the vector. Sergent and his co-workers (1910–11), and later Nicolle, Blaizot, and Conseil (1912), as a result of a series of researches, reported that they were able to infect monkeys with crushed lice which had been taken from cases of relapsing fever.

Ticks.—The following species of ticks are either suspected or proved carriers of relapsing-fever spirochetes:

Ornithodorus moubata infests native dwellings and resting places along caravan routes of South and Central Africa. They are night biters and, although man is the preferred host, they are also known to take blood from a few of the lower animals. In Africa this tick may be found in an area ex-

tending southward from latitude 10° North, and eastward from longitude 10° East. This includes Southern, Eastern, and a part of Central Africa. *Ornithodorus talaje* carries the relapsing fever spirochete of Panama and has a wide distribution in Central and South America. It may be the chief carrier of the disease in these countries. *Ornithodorus venezuelensis* has been considered a carrier of relapsing fever in Columbia and Venezuela, *Ornithodorus savignyi* in Africa, India, Arabia, and Tunis. *Argus persicus* has been considered a probable carrier. This tick is almost cosmopolitan in its distribution, but is incriminated as a carrier of relapsing fever in Persia and Palestine only.

Morbid Anatomy.—There is no characteristic postmortem finding except the possible presence of spironema in smears taken from the spleen and bone-marrow. The internal organs show evidence of toxemia, and they may be more or less deeply stained with bile. The spleen commonly shows a few infarcts. Some particular organ may show some special complication, such as pneumonia, an acute dilatation of the heart, edema of the brain, or perhaps spirochetal emboli and thrombosis of the cerebral vessels. Hemorrhage may be found in the nose, ear, stomach, intestines, uterus, or kidneys.

Symptoms.—The INCUBATION PERIOD is usually under twelve days; the average is seven days.

PRODROMAL SYMPTOMS.—Prodromal symptoms are unusual, but in some the onset may be marked by mental depression, lack of activity, slight shivering, and sweating.

THE ATTACK.—The patient is suddenly seized with a chill or, more usually, a chilliness lasting from fifteen minutes to several hours, mounting fever, frontal headache of the "hammering" type, nausea or vomiting, perhaps of a bilious character, and a giddiness which compels the patient to take to bed.

The course of the attack may be marked by prolonged spells of shivering, excessive vomiting, and subsequently an intense thirst. Pain in the epigastrium or in the hepatic region may be a complaint. Muscular and joint pains, particularly in the thighs, shins, and wrists, may be excruciating. Occasionally the subject experiences a burning sensation all over the body.

The patient at this stage is usually found shivering under blankets; the face flushed and expectant; the skin hot; the thermometer registering 104° F. or perhaps higher, and an increased pulse rate consistent with the height of the temperature. A slight icterus of the conjunctiva may be observed, the tongue is centrally coated with a white fur, the liver slightly enlarged and tender, and the spleen easily palpable.

This attack lasts several days (usually two to seven). The symptoms may steadily increase in severity to a crisis, which usually declares itself by a rapid falling of the temperature to normal or subnormal, a slowing of the pulse, and profuse sweating. The crisis brings with it a complete and miraculous restoration of health. Ordinarily, however, it is not the end of the disease, but of one paroxysm. This attack is succeeded by the second stage of the infection, the afebrile interval.

AFEBRILE INTERVAL.—The afebrile interval is generally characterized by a state of normal well-being. In the days prior to specific treatment it was difficult to persuade the patient that the course of the disease had not yet ended. In some, however, nausea and vomiting may persist. Occasionally marked weakness or even prostration may follow the initial attack.

After a duration of about one week (two to sixteen days, sometimes longer) this stage is ended by a relapse.

Relapse.—Because of the specific curative action of salvarsan the occurrence of a relapse in a treated case is no longer characteristic. However, in an uninterrupted case, a relapse may occur in from one to thirteen days after the crisis of the first attack. The symptoms now present may be exactly the same as those initiating the attack, but it is usual for them to be less severe and of shorter duration. A second relapse is uncommon; a third, rare. Incidences of many relapses have been recorded.

Special Features.—*Skin.*—A macular rash in the initial attack, not unlike "rose-spots," may occur and persist from a few hours to several days. Jaundice is occasionally met with. Beyond a slight icterus, however, it is not common. Jaundice develops comparatively late in the course of the disease. Edema of the face and hands suggestive of nephritis may occur in a small minority of cases. Edema of the extremities has also been noted.

Gastro-intestinal Tract.—*Vomiting* may begin during a paroxysm and persist through several days of the afebrile period. It may be of a bilious character, or it may even resemble the black vomit of yellow fever. *Constipation* is usual, but *diarrhea* may develop during a paroxysm or immediately following a crisis. Diarrhea is frequent in Central and Southern African "tick fever" and not uncommon in the Asiatic variety. *Hemorrhage* from the bowels or stomach may mark the crisis of an attack.

Tympanites, especially in the toxic cases, may occur. *Hiccup*, more frequent in the Asiatic relapsing fever, has also been observed in the relapsing fevers of other parts of the world.

Nervous and Mental Symptoms.—The mind is usually clear. In a certain number of cases, however, there may be mental symptoms varying from slight dulness to well-marked and even violent delirium. In the severely toxic, a typhoid state may supervene. Facial paralysis of an evanescent character is occasionally observed.

Pulmonary Symptoms.—*Cough* and *slight bronchitis* are noted in many cases, and occasionally, in the severely toxic, signs of pneumonia may be present. Dyspnea occurs occasionally. A dry pleuritic rub is present infrequently.

The Eyes.—Beyond a mild conjunctival injection, eye affections are unusual in the majority of cases. A postfebrile ophthalmitis may occur several weeks or months after recovery.

The Urine.—Albuminuria during the paroxysm is usual, but is without especial significance.

The Blood.—A leukocytosis occurs during the paroxysms, with the neutrophils slightly predominating.

Diagnosis.—Specific.—The diagnosis is easily established by the finding of the causative organism in the blood *during a paroxysm*. For this purpose a drop of fresh blood examined under the high-power microscope, illuminated either by direct or oblique light rays (dark field), will usually demonstrate the parasite. A direct smear of the blood dried and stained by one of the polychrome stains (Wright's, Hastings', etc.) is also a good method. In mild attacks the spirochetes may be so scanty as to require a thick smear or a prolonged search of thin preparations for their discovery.

Differential.—Sporadic cases of relapsing fever are frequently con-

fused with *malaria;* in fact, the differential diagnosis is usually made in the laboratory upon the finding of the spirochete in blood-smears.

In epidemics, *typhus* and *relapsing fevers* very frequently coexist and are often confused. Certain well-marked clinical differences, together with the laboratory findings, should make the differentiation easy.

Dengue, smallpox, trench fever, infectious jaundice, yellow fever, typhoid fever, influenza, and pneumonia present in their courses a few symptoms in common with relapsing fever, but offer no especial difficulty in their differentiation.

Prognosis.—The disease tends to be self-limiting. Each relapse is usually less severe than that preceding. In the course of an uninterrupted attack of the infection it is not uncommon for a mild abortive attack to signal the beginning of recovery.

The infection in a strong, robust subject is not especially dangerous. In a weak, poorly nourished individual, however, it may be fatal. The case mortality for the European variety caused by *Spirochæta recurrentis* (Obermeieri) is about 4 per cent. In India and Africa a mortality of 30 to 40 per cent. has been recorded. Unfavorable signs are sudden syncope, acute cardiac dilatation, suppression of urine, convulsions, coma, and severe toxemia.

Immunity.—An *uninterrupted* attack of relapsing fever confers a partial or complete immunity to reinfection with a spirochete of the same species. This immunity is generally considered to be of short duration. Animals may be immune to reinfection for many months. Reinfection in man has been reported as early as two months. Natives of relapsing-fever districts possess a partial or complete immunity to the infection.

Prevention.—In the infected districts tick-transmitted *relapsing fever* may follow a night spent along caravan routes, especially when native huts have been occupied. Careful inquiry as to the prevalence of the disease and avoidance of unduly close personal contact with the sleeping quarters of natives minimizes the liability of infection.

Treatment.—Before Erhlich's epochal experiments with *salvarsan* on various spirochetes, including those of relapsing fever, no medical treatment prevented a relapse in this disease. The effect of arsphenamin in ending an infection of relapsing fever is as magical as it is in clearing up the repulsive lesions of yaws. The drug should be given intravenously in dosages of about one-half that recommended for the usual therapeutic purposes, 0.2 to 0.3 gm. It is most effective at the *beginning* of a paroxysm. Occasionally a full therapeutic dose will be required to end the infection. In about 80 per cent. of the cases one injection of 0.3 gm. salvarsan or 0.45 gm. neosalvarsan will eradicate the infection. However, it is advisable to keep the patient under observation for a period of fourteen days following apparent recovery.

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YELLOW FEVER

Definition.—Yellow fever is an acute infectious disease characterized by sudden onset, moderately high fever, acute parenchymatous nephritis, profuse hemorrhage from the mucous membranes of the alimentary tract, and

jaundice. The height of the disease is reached within a few days, and in nearly 60 per cent. of cases the infection is fatal. Convalescence is usually rapid, and a single attack confers a lasting immunity. The outstanding clinical features of fully developed cases are the early progressive acute nephritis, jaundice, relatively slow pulse, and the vomiting of altered blood known as *black vomit*.

Incidence.—Yellow fever is not contagious, and it is transmitted only through the bite of a domestic mosquito, *Aëdes ægypti* (or *Stegomyia calopus* or *S. fasciatus*), which has sucked the blood of a yellow fever patient during the first three or four days of the disease. It is easy to understand now why yellow fever prevailed unchecked among non-immune persons in the past when the rôle of the mosquito was not known. The disease was endemic in tropical regions because of a continuous and undiminished supply of *Aëdes* mosquitoes; it visited temperate zones or high altitudes only during the warm season, when the mosquito propagated. During the era of traffic by sailing vessels, when the water-supply was carried in open tanks—the type of breeding-place selected by the female *Aëdes*—there was ample opportunity for transportation of infected mosquitoes from endemic foci in the tropics, and an epidemic of yellow fever was possible in any part of the world where the mosquito was present to convey the virus thus furnished. In fact, during the eighteenth and nineteenth centuries epidemics of yellow fever occurred as far north as Pennsylvania, New York, Massachusetts, Nova Scotia, Spain, Portugal, France, and England. Following the demonstration of the part played by the *Aëdes*, the temperate zones were protected by quarantine, and during the last twenty years most of the endemic centers have gradually been freed of yellow fever by systematic antimosquito measures. The United States saw its last visitation in New Orleans in 1905. During the early days of mosquito control, destruction and petrolization of breeding-places were the principal means of reducing the number of mosquitoes (Havana, Panama, Rio, Para), but in recent years it has been found that there are several varieties of small fish which feed voraciously upon mosquito larvæ, and their use as larva destroyers has proved to have many advantages (Guayaquil, Peru, Mexico, Central America). At the end of 1923 certain limited areas in Brazil and West Africa were the only places where yellow fever was still occasionally to be found. The disease stands out as perhaps the most conspicuous example in medical history of an acute infectious disease which can be controlled and exterminated by rational sanitation.

Etiology.—Yellow fever is caused by a specific micro-organism, *Leptospira icteroides*, first isolated in 1918, during an epidemic of yellow fever in Guayaquil, Ecuador. The organism is present in the circulating blood of the patient at least during the first three or four days of illness, and is occasionally found in the liver or kidney at autopsy when the patient has died early in the disease. It is absent from the "black vomit" and feces. The organisms are never numerous in the blood-stream and are seldom present in numbers large enough to permit detection by microscopic examination; as much as 1 to 2 c.c. of blood may be required to transmit the infection by direct injection to non-immune persons or susceptible animals. *Leptospira icteroides* is capable of passing through the pores of a Berkefeld filter, but not through the finer grade of Chamberland filter. It survives about five days outside the human body in citrated blood kept

at room temperature under a layer of paraffin oil. It is killed by heating to 50° C. for ten minutes. When ingested by *Aëdes* females it gradually multiplies, and in a tropical climate the mosquito is rendered infective in about twelve days and remains infective during the remainder of its life. *Aëdes* mosquitoes have been kept alive as long as five months in the laboratory, and there has been one instance in which a mosquito was still infective fifty-nine days after the infecting meal. It is not known whether or not the organism undergoes a life-cycle in the body of the mosquito. The offspring of the infected mosquitoes do not inherit the infectious agent.

Of the various other micro-organisms to which an etiological relationship has been ascribed, none have reproduced the symptoms and lesions of yellow fever or shown the characteristic properties of the yellow fever virus which Reed and his collaborators determined early in their studies, and all have eventually proved to be ordinary skin cocci, paratyphoid bacilli, or artefacts. For the detection and isolation of *Leptospira icteroides* the dark-field microscope and special cultural, staining, and immunological methods are essential. More recent investigations in Mexico, Peru, and Brazil have confirmed the etiological relationship of *L. icteroides* to yellow fever.

Bacteriology.—*Leptospira icteroides* is an extremely delicate, actively motile, filtrable micro-organism, measuring in length about the diameter of a red blood-corpuscle, sometimes somewhat longer; its width is less than that of *Treponema pallidum*. The entire body is closely wound like a rope; both extremities are drawn out to fine points and are usually bent like a hook. The organism is invisible under ordinary bright-field illumination, but is readily detectable by means of the dark-field or ultramicroscope.

Leptospira icteroides can be isolated either from the blood of yellow fever patients during the febrile stage, or from the blood, liver, or kidneys of animals (marmosets, guinea-pigs) experimentally infected with the blood of yellow fever patients. It is present in such small numbers in the peripheral blood that its direct detection microscopically is extremely difficult and its transmission to animals inconstant; most laboratory or domestic animals are completely refractory to infection with the organism. Young guinea-pigs reared in a temperate climate are moderately but not uniformly susceptible, and marmosets and young puppies can be infected by injecting large quantities of recently isolated cultures. In the Brazilian "prego" monkey, *Cebus macrocephalus*, inoculation of a recently isolated strain resulted in the reproduction of the complete clinical and pathological picture of human yellow fever.

The organism is a strict aërobe and can be cultivated only in a medium containing suitable blood-serum, preferably that of man or rabbit. Unlike various pathogenic bacteria, *Leptospira icteroides* grows well and remains viable for many months at room temperature; hence it is capable of living almost indefinitely in the mosquito body, where the requisite blood constituents are continuously and amply supplied. Its growth at ordinary summer temperatures is slow, however, and does not attain its maximum until after a lapse of ten to twelve days—a period corresponding to that designated by Carter as the "extrinsic incubation period" of yellow fever. It has been shown that virulent leptospiras are present in the bodies of *Aëdes* mosquitoes which have been allowed to feed on yellow fever patients or experimentally infected animals.

Leptospira icteroides is a fastidious organism; it readily perishes upon drying or in acid or alkaline media, and it is rapidly destroyed in material contaminated by putrefactive bacteria; hence the innocuousness of yellow fever fomites, black vomit, or feces as demonstrated by the Yellow Fever Board as early as 1900.

The blood-serum of yellow fever convalescents gives specific immunity reactions (Pfeiffer phenomenon, agglutination) with *Leptospira icteroides.*

Morbid Anatomy and Physiology.—The pathological changes in yellow fever are due to direct invasion by *Leptospira icteroides* of certain visceral organs for which the organism exhibits a special preference. The liver, the tubular portions of the kidneys, and the general capillary vascular system are principally affected. The organism undergoes only temporary multiplication in the circulating blood until it finds its favorite localities, the liver and kidney, where it establishes itself and increases. It invades the protoplasm of the liver cells and that of the renal epithelia, causing first swelling and fatty degeneration, and eventually necrosis of the parenchymatous cells. In the liver, ruptured biliary capillaries in necrotic areas soon communicate with the lymph spaces, and the bile finally enters the general circulation, producing the characteristic jaundice, cholemia, and bile-stained urine. The common bile-duct shows no obstruction, and the feces in yellow fever is usually bile stained. In extensive necrotic areas, very often affecting the middle zone of the lobules, the liver cords are disturbed, and the rounded liver cells undergo peculiar acidophilic changes. In moderately severe cases the necrosis is less extensive, but the fatty infiltration of the protoplasm is very striking. The liver is not perceptibly increased in volume. Its color is pale yellow or yellowish brown, occasionally greenish brown.

The changes in the kidneys are confined chiefly to the renal epithelia, which may become fatty and necrotic; the tubules are often filled with detached epithelia or granular casts. The early and progressive albuminuria, the abundant casts, and the final anuria observed in fatal cases can readily be explained by the wholesale tubular blocking. Lime casts have been frequently found in the kidneys and are regarded by W. H. Hoffmann as of diagnostic significance.

One of the most striking symptoms in yellow fever is the tendency to hemorrhage. The "black vomit" and the tarry stools typical of the disease are due to rupture of the capillaries of the gastro-intestinal tract. The "coffee-ground" or "black" gastric contents is acid in reaction and consists of blood altered by the gastric secretion, detached granular cell débris, fat globules, and half-digested food particles; it may occasionally be the color of port wine because of admixture with fresh blood; rarely, bright red. Macroscopically, the mucosa shows arborization of the capillaries and hemorrhagic areas of varying dimensions. The gland cells are little altered. Similar changes occur in the intestines. Peyer's patches are prominent and sometimes hemorrhagic, and there may also be hemorrhages on the serous surfaces of the intestines.

The heart is flabby, and hemorrhages occur in the endocardium, epicardium, or myocardium. Fatty changes in the muscle-fibers have been reported.

The changes in the lungs and pleuræ are mainly hemorrhagic in character; infarcts have occasionally been observed. In most instances the lungs appear normal; sometimes they are edematous.

Bloody effusions into the subconjunctival or subpleural tissues or under the capsules of the liver and kidney have been frequently found. Petechiæ or hemorrhagic blotches on various parts of the body are not uncommon.

The adrenal glands are hyperemic and sometimes show hemorrhage and fatty degeneration of the cells. The spleen and lymph glands, usually normal in size, may be hyperemic.

The character and distribution of the lesions produced in susceptible animals by means of pure cultures of *Leptospira icteroides* are practically identical with those of human yellow fever.

Symptoms.—The *incubation period* is usually three to six days, the minimum reported is two days and one hour, and the maximum twelve days. The course of the disease may be divided into three stages: the initial period (stage of invasion); the period of specific manifestations; and, in non-fatal cases, the period of convalescence.

The *initial stage* is characterized by sudden onset, with or without chills, accompanied by severe frontal headache and general muscular pains, which are especially intense in the lumbar region and limbs. Special reference is often made to the aching of the calves, the so-called *coup de barre* of the French authors. There is moderate fever—102° to 103° F.—which usually increases until the temperature reaches 104° F. within twenty-four hours. The face is flushed, the conjunctivæ strikingly injected. There is loss of appetite, anxiety, and usually insomnia. Nausea and thirst are frequently present, and vomiting of bile-stained food may occur. The tongue is clean and red along the borders and tip, but the dorsal surface is coated. The gums are congested. Sometimes there is epistaxis. In the majority of cases the fever drops considerably after twenty-four hours (period of remission), and slight traces of albumin appear in the urine. The relief which the patient may feel at this time gives a false idea that the case is a mild one. The remission may last a few hours or as long as twenty-four hours; then the disease enters the *second stage*, with all its characteristic manifestations. The temperature rises again to 103° or 104° F.; there is intense thirst and gastric irritability which leads to incessant nausea and vomiting. Epigastric and lumbar pains are usually complained of. The urine contains albumin and casts in large quantities and diminishes in quantity as it gains in depth of color. The conjunctivæ are still injected, and the scleræ have become somewhat jaundiced. Whatever is ingested is thrown up, and in the fluid vomitus dark particles of altered blood now appear—the so-called "fly wings," a forerunner of the "black vomit." Blood may be expressed from the swollen gums and epistaxis may often last for hours.

On the fourth day all the symptoms are aggravated, and the typical picture of severe yellow fever is complete: the uncontrollable "black vomit," the bleeding gums, parched mouth, more or less yellow coloration of the entire body, loose tarry feces, paroxysms of hiccup, and profuse epistaxis. The urine is dark, with yellow foam, scanty in quantity, and full of epithelial or granular casts; some erythrocytes and leukocytes are found in the sediment. It may contain 5 gm. of albumin per liter; sometimes so much is present that the urine solidifies on boiling. In such cases death may occur at any time after the fourth day, usually by the seventh day. Anuria precedes death in most instances. The temperature gradually falls to normal or subnormal; occasionally, in fatal cases, there is a sudden rise just before death.

In severe but non-fatal cases a favorable prognosis is first indicated by the restoration of renal function, *i. e.*, increase in the volume of urine and decrease in its content of albumin, casts, and bile pigments which begins on the fourth, fifth, or sixth day. In moderately severe cases the symptoms that follow the remission are less acute and intense, particularly the urinary disturbances, and the "black vomit" may or may not appear, although jaundice is usually present.

Convalescence, once begun, proceeds rather rapidly, and the patient who has had a severe attack may recover within a month. In mild cases convalescence may begin soon after the initial stage, all symptoms, including albuminuria, beginning to subside on the third or fourth day.

The *pulse* in yellow fever is rather characteristic, its rate in respect to temperature being relatively slow—90 for a temperature of 104° F., 80 for 103° F., 70 for 102° F., etc. This relative bradycardia is known as Faget's sign.

To sum up, then, yellow fever is a disease of comparatively short duration, the febrile stage lasting three to four days, during which there may be a remission, followed by the appearance of three cardinal symptoms—hemorrhage (especially the "black vomit"), jaundice, and acute parenchymatous nephritis. Death ensues within the next two to four days, or the crisis is reached in seven to eight days from onset; very few patients die after having passed this period. In severe cases jaundice and albuminuria may persist for several weeks after all other symptoms have disappeared. The average period of convalescence is two to four weeks, and there is complete restitution of the liver and kidney functions.

Complications are rare. A second rise of temperature at the end of the second week has occasionally been reported, and parotitis has sometimes been observed.

Diagnosis.—The cardinal symptoms are usually sufficient to decide the nature of the disease when it occurs in a yellow fever area. In mild form and in its early stages, however, yellow fever may be confused with several other diseases.

Malaria must be differentiated from the early stages of yellow fever by examination of the blood, although a yellow fever patient may also have malaria. In the second stage there is no confusion with malaria.

The initial symptoms of *dengue* are somewhat similar to those of yellow fever, but after two or three days the characteristic eruption of dengue and the absence of jaundice, albuminuria, and "black vomit" are sufficient to differentiate it. The spleen is enlarged in dengue, but not in yellow fever.

Infectious jaundice, or Weil's disease, is most difficult to differentiate from yellow fever. The symptom complex is practically the same, but in Weil's disease the evolution of symptoms is slower. At one time both diseases were very common in the tropics, and the recognition of infectious jaundice became definite only after a region had been freed of yellow fever by antimosquito measures. Where there are no *Aëdes* mosquitoes a disease resembling yellow fever is usually severe infectious jaundice. Convalescent serum from yellow fever gives a positive Pfeiffer reaction with *Leptospira icteroides*, but not with *Leptospira icterohæmorrhagiæ*, the causative organism of infectious jaundice, and *vice versa*; this mode of differentiation has been used in some tropical districts where cases occurred which might be either yellow fever or infectious jaundice.

Influenza and *measles* have occasionally been mistaken for yellow fever by competent persons, but the course of disease in the one and Koplik's spots in the other decide the issue.

Prognosis.—The early appearance and subsequent steady increase of albumin in the urine, together with a gradual decrease in the volume of urine, is the most serious prognostic sign; early jaundice and a small and rapid pulse, not characteristic of yellow fever, are also omens of gravity. In the second stage a rapid fall of the temperature to subnormal, with a sudden increase in the pulse rate, usually presages death. "Black vomit" and other hemorrhagic symptoms are not of prognostic significance.

Treatment and Prevention.—The *specific treatment* consists in the early administration of *anti-icteroides* immune serum in sufficient quantity. This is a polyvalent antiserum prepared by injecting into horses cultures of *Leptospira icteroides*. It has been used in about 150 cases, with reduction of the mortality from the usual 50 or 60 per cent. to 10 or 15 per cent. Due precautions must be taken to avoid anaphylactic reactions, and it is desirable to give a preliminary intravenous injection of 1 or 2 c.c. of the serum; if no ill effects follow within one hour, a full dose, 25 c.c., may be administered intravenously. The dose may be repeated in severe cases after six hours.

The *usual symptomatic treatment* and proper nursing should accompany the serum therapy. Absolute rest, no food, and abundance of water—Carter's principles of yellow fever treatment—are essential. Transportation of the patient from one place to another is hazardous, and aggravates the nephritic condition, precisely what must be avoided in any case suspected of being yellow fever.

The serum treatment must be begun as early as possible. After the first three or four days of illness, when the patient has reached the stage of uremia and cholemia, and there are severe hemorrhages from the mouth, nose, and gastro-intestinal tract, there is little or no chance of benefit from the administration of the antiserum.

Besides the *isolation of patients* by screening, and the destruction of *Aëdes* mosquitoes, *prophylactic vaccination* offers another means of preventing yellow fever. The principle is similar to that used in the case of typhoid fever and consists in the inoculation of a killed culture of *Leptospira icteroides*. Rich cultures, containing 2,000,000,000 organisms per cubic centimeter, are used in preparing the vaccine, which is administered in two doses of 2 c.c. each, four to six days apart. When the site of inoculation is thoroughly massaged after the injection no unpleasant local or general reactions occur. The development of immunity requires a period of ten to fifteen days, and the duration of protection is probably not longer than five or six months. Comparison of case incidence among vaccinated and unvaccinated persons during epidemics of yellow fever in Ecuador, Mexico, Guatemala, and northern Peru has shown that vaccination confers protection against the disease in the majority of instances.

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WEIL'S DISEASE

(*Infectious Jaundice, Spirochetosis Icterohæmorrhagica, Epidemic Jaundice*)

Definition.—Weil's disease is an epidemic disease characterized by abrupt onset with fever, jaundice and enlargement of the spleen, and by the presence of the *Spirochæta icterohæmorrhagiæ* in the blood.

History.—In 1886 Weil first called attention to the disease which he thought might be merely an atypical form of some known infection such as typhoid. Epidemics have, however, been frequent during military campaigns (Boer War, World War).

Etiology.—The disease occurs most frequently in early life, and much more often in males than in females. It is particularly common in soldiers in garrisons and trenches. The Japanese observers noted it in miners and emphasize the important influence of dampness in the mines. They discovered the specific cause in 1914 and named it *Spirochæta icterohæmorrhagiæ*. The organism is present in the blood in the early stage of the disease, and in the urine after the fifteenth day. It is stained by Giemsa and appears as a spiral with from two to fifteen coils. The *Spirochæta icterohæmorrhagiæ* is present in rats the world over, and it is probable that this rodent is the source of infection, possibly through the medium of some insect, but proof of this is still lacking. American investigators have recently brought forward considerable evidence suggesting that a non-spirochetal form of epidemic jaundice exists.

Morbid Anatomy.—The liver is firm, deep yellow in color, and unchanged in size. The liver cells are swollen, but undergo little demonstrable histological change. The renal lesions consist of cloudy swelling, or even necrosis of the tubular epithelium, with exudation into the interstitial tissue. Areas of hyaline degeneration and necrosis in certain skeletal muscles, particularly of the calf, have been described. The spleen is sometimes enlarged and contains fragments of red corpuscles and deposits of

hemosiderin. Similar deposits are found in the liver and bone-marrow. The biliary staining of the tissues common to all forms of jaundice is present. Whether the jaundice is due to obstruction of the bile capillaries as a result of edema of the liver, or to destruction of blood in the spleen, in Kupffer's cells in the liver, and in the bone-marrow is not definitely known.

Symptoms.—The onset is sudden, often with chills followed by fever, nausea and vomiting, and myalgic pains all over the body, especially in the calf muscles. In severe cases epistaxis, oozing of blood from the gums, and subconjunctival hemorrhages may occur. In other cases signs of meningeal irritation, such as stiffness of the neck, headache, and Kernig's sign, appear. The total quantity of urine is reduced and albumin, casts, a few red cells, and a large quantity of urobilin are present. The amount of non-protein nitrogen in the blood is increased.

Jaundice becomes evident in three to six days, bile appears in the urine, and the liver is often tender. The other symptoms begin to improve and ten days after the onset the temperature is usually normal. Relapses are not infrequent and the slow convalescence is marked by depression, weakness, and anemia.

Diagnosis.—Weil's disease is distinguished from *yellow fever* by its milder symptoms and less pronounced renal signs. The most reliable differential test, however, is the demonstration of the spirochete by injection of blood into guinea-pigs. From *acute yellow atrophy* it differs particularly in its clinical course, the absence of atrophy of the liver, and in its epidemicity.

Treatment.—Specific.—Vaccination with killed cultures is said to protect guinea-pigs and man. Immune serum from inoculated horses has also been used as a curative measure, with possible success. The value of these specific agents has not been proved, however, and the main treatment is still symptomatic.

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SYPHILIS

Definition.—Syphilis is a specific infectious disease of protean manifestations caused by the *Treponema pallidum*. It may be acquired or congenital. The *acquired form* is characterized by an initial sore and an early stage of invasion with relatively mild systemic disturbance and by eruptions upon the skin and mucous membranes. After a variable interval there follows a late stage of specific granulomata, connective-tissue proliferation with destruction of parenchyma, and disturbance of the function

of various organs. The *congenital form* is similar in its pathology, except that there is no primary lesion and the late manifestations predominate.

History.—There are two opposing views concerning the antiquity of syphilis. One is that the disease was introduced into the civilized world in relatively recent times by the returning sailors of Columbus, and that it was spread throughout Italy in 1493 by the soldiers of Charles VIII. It was about this time that the disease became a great scourge and spread rapidly over Europe. The other view is that syphilis is a very ancient disease which has existed among civilized peoples since the very dawn of history. Early Egyptian and Assyrian inscriptions as well as the bony changes found in mummies are cited as documents in evidence. It is even said that a Chinese medical treatise written more than twenty centuries before the Christian era contains direct reference to the disease. According to this view the great epidemics of syphilis which occurred during the Middle Ages were mere recrudescences of an already endemic disease. This latter view seems the more probable.

The syphilis of the Middle Ages was virulent and wide-spread. Its rapid propagation at this time was effected by various modes of personal contact, and its venereal origin was not generally recognized. Later syphilis came to be regarded solely as a venereal disease; but the hard chancre, the soft chancre or chancroid, and gonorrhea were not distinguished for a long time. They were finally differentiated by Ricord.

Then there came in the nineteenth century a period when syphilis was studied largely in its dermatological aspects. Although the dermatologists of that day (Ricord, Hebra, Fournier, and others) understood the general character of the infection, the graphic appearances on the skin and mucous membranes seemed in their minds to dominate the clinical picture and to give the disease special dermatological interest.

In the early part of the twentieth century the conception of syphilis was greatly broadened and the disease gradually assumed a different clinical aspect. Experimental study was facilitated by the discovery of Metchnikoff and Roux that syphilis can be transmitted by inoculation to the lower animals. In 1905 Schaudinn made the epoch marking discovery of the causative agent, the *Treponema pallidum*. About a year later Wassermann devised the biological reaction of great diagnostic value to which his name has been given. In 1910 Ehrlich in his studies in chemotherapy succeeded in producing the highly potent remedy salvarsan (arsphenamin). Finally in 1913 the much discussed question of "parasyphilitic" diseases was settled by Noguchi when he demonstrated the constant presence of the treponema in the brain of paretics. As the result of these discoveries syphilis is today considered neither a venereal nor a skin disease, but a general disease with protean manifestations.

Incidence.—Estimates of the rate of incidence of syphilis are varied. The disease is wide-spread, but is not as prevalent in the United States as in Europe. Hazen thinks that 10 per cent. of American adults have syphilis, but this estimate is probably too high. Of 2000 consecutive patients who came to the office of the author, 5 per cent. gave a positive Wassermann reaction. Hospital statistics show that the incidence of positive Wassermann reactions is between 8 and 15 per cent. Syphilis is much more common among negroes than among the whites. In the Hillman Hospital at Birmingham 8 per cent. of the white patients and 25 per cent. of the negroes presented evidences of syphilis.

Etiology.—The *Treponema pallidum* was first discovered by Schaudinn and Hoffman in the tissue fluids of an initial syphilitic lesion. Subsequently its causative relation to syphilis was abundantly proved both by these investigators and by others. Koch's postulates have been fulfilled. The treponema is a delicate spiral, "corkscrew" organism, 6 to 20 micra in length, actively motile, and difficult to stain. It can perhaps best be classed among the protozoa, although Schaudinn suggests that it may represent a transition stage between the protozoa and the bacteria.

The parasite is found in abundance in the tissue fluids and secretions of the primary lesion. During the early stages it is present in large numbers in the lymph-nodes, particularly in those nearest the initial sore. Later it may be found in the roseola and other skin lesions as well as in the inner organs. During the so-called secondary stage it has been found in both

blood and spinal fluid. Treponema have been demonstrated in the scars of syphilitic lesions long after healing. The apparently healthy tonsils of untreated syphilitics have been shown to harbor the organism in abundance. In general it may be said that during early syphilis there is an invasion of the entire body, so that treponemata are present in abundance in practically all of the organs; in late syphilis the infection is more localized, and smaller numbers of the organism are found in the parenchyma of the diseased organs. Treponema can seldom be found in the specific granulomata of the late stages, but are encountered in relatively small numbers in the apparently healthy surrounding tissue. They are found in greatest abundance in the tissues and organs of patients with congenital syphilis.

The treponema is best studied in the living state. It can be obtained in the fluid which exudes from the base of a primary ulcer after it has been swabbed clean, and scraped, or in other fluids expressed from syphilitic tissues. In a preparation of this fluid upon a glass slide, the dark-field illuminator and an oil immersion lens will reveal clearly the delicately spiral forms and their characteristic gliding motility.

The *Treponema pallidum* stains poorly with the ordinary aniline dyes. The most satisfactory stained preparations are dried smears made from tissue juices and stained with *Giemsa's solution*, or by the *Fontana method* ($AgNO_3$). *India-ink* is a satisfactory and often used type of stain. A drop of tissue juice is mixed with a drop of Günther India ink, spread thin on a slide, and then permitted to dry. In such preparations the organism, when viewed with an oil immersion lens, appears as a white spiral on a black background. The treponema can be stained in tissue sections by means of the *silver impregnation method* of Levaditi. This technic has greatly advanced our knowledge of the pathology of syphilis.

It has been suggested that there are several distinct strains of treponemata, each of which has special tissue affinities—neurotrophic, dermatotrophic, etc. The localization is, however, probably determined not so much by the special characteristics of the invading organism as by the defense or lack of defense offered by the various organs.

Outside the body the treponema dies quickly. It is rapidly destroyed by ordinary soap. It is extremely difficult to grow, especially in pure culture, but Noguchi has finally succeeded in propagating the organism under anaërobic conditions in a medium of horse-serum which contains particles of animal tissue.

Modes of Transmission.—Syphilis is most often transmitted by sexual intercourse, but other forms of personal contact, such as kissing, the nursing of an infant by an infected wet-nurse, or the examination by the physician of an infected patient, also spread the disease. Shamberg states that one young man with a chancre on the lip infected 8 young women with syphilis by kissing. Although extragenital chancres may be found on any part of the body, they are usually located on the lip and the finger. Before the days of rubber gloves, physicians were occasionally infected by examination of a patient. Indirect contact, such as comes from the use of a common instrument by glass blowers, musicians, etc., or a common drinking cup, is sometimes a mode of transmission. The extragenital chancre is particularly dangerous because its true nature is often unrecognized and no precautions are taken to prevent transmission. In localities where syph-

ilis appears to be endemic and to afflict almost the entire population the extragenital method is probably the most common form of transmission. It is said that there are Russian villages in which the whole population is infected and in which the disease has completely lost its venereal character. Infection most often results from contact with the chancre or mucous patch, although it can be derived from almost any syphilitic manifestation. The earlier the lesion, the greater the chance of infection.

The treponema is believed by many to produce invariably an initial sore at the point of entrance, but there is good evidence that at times it passes through the apparently unbroken skin without producing a chancre. The author has seen a case of typical early cutaneous syphilis in a physician, which developed shortly after he had scrubbed from his hands, with a rough brush, the blood of a patient with a florid syphilitic roseola. There had been no chancre on the hands or elsewhere and, so far as could be ascertained, no other exposure to the disease.

Congenital syphilis is transmitted by the mother. If the infection originally comes from the father, the mother is first infected, and then, after acquiring the disease, transmits the treponema through the placenta to the fetus.

Morbid Anatomy.—The primary sore or chancre is a local inflammatory lesion characterized by infiltration with lymphocytes and plasma cells; these cells accumulate in the tissues and around the blood-vessels and block the lymph vessels. Epithelioid cells and occasional giant-cells are also present, and there is proliferation of the connective tissue. The blood-vessels are often narrowed and obliterated by proliferation of the lining cells and by the inflammatory reaction which begins in the adventitia. This obliteration of arteries, veins, and lymph vessels is especially characteristic of syphilis. Interference with the blood-supply leads to retrogressive changes. Finally only a scar remains.

Even before the chancre has fully developed the treponema invades the neighboring lymph channels and thence finds its way into the general circulation. Local lymphangitis and lymphadenitis are, therefore, early lesions. The roseola and other skin manifestations which develop a little later represent a reaction of the skin to the presence of the treponema. There is first a congestion of the small vessels of the papillæ, then passage of the organism into the tissues, and finally perivascular round-cell infiltration.

Other so-called secondary lesions may be found in any of the organs. Obliterative arteritis as well as phlebitis and round-cell infiltration accompanies all the early changes. At this stage, the fixed tissues, with the exception of the vessels, are not extensively destroyed.

In late syphilis, on the contrary, not only are the vessels involved, but there is extensive destruction of parenchyma with an overgrowth of fibrous tissue. This chronic interstitial inflammatory reaction presents no peculiarly characteristic features except perhaps the invariable obliterative arteritis and phlebitis. Diagnosis is often facilitated, however, by the presence of the gumma—the characteristic lesion of late syphilis.

The gumma is a granuloma or conglomeration of granulomata in the formation of which an infiltration of lymphocytes and a few epithelioid and plasma cells play the chief rôle: connective-tissue proliferation, obliterative endarteritis, phlebitis, and necrosis also take place. The gumma

is often soft in the center and exudes semisolid débris. It may be of almost microscopic size, or a large tumor several centimeters in diameter. After it breaks down scar tissue usually forms.

The most characteristic histological feature of syphilis is the involvement of the blood-vessels. This consists at first of an intense round-cell infiltration in the adventitia and in the *vasa vasorum*, which may spread evenly along the vessel wall or may appear as irregularly placed nodules. All three coats partake of this inflammatory process. There is a deposit of hyaline tissue in the intima with fibrous changes in the media. Disorganization of the normal elastic and muscular structure leads to weakening of the vessel wall and often to the formation of aneurysms. The smaller vessels become obliterated. All syphilitic lesions are said to have their beginning in the walls of the blood-vessels.

The Course of Syphilis.—From the very beginning syphilis is a general disease in which the entire body is involved. The treponema enters through the skin or mucous membrane and produces at the point of entrance a characteristic tissue reaction—the chancre or papule. An abrasion or other lesion favors, but is not essential for infection, for the organism can unquestionably enter the apparently unbroken skin. As has been said, there is overwhelming clinical evidence that infection does occasionally occur when no initial lesion can be found; but whether the lesion actually fails to develop or merely escapes notice is a matter of dispute.

The chancre appears within from ten to sixty days after infection, usually after about three weeks. Even during this "*first incubation period*," before the ulcer can be seen, the infection begins to spread throughout the body. The treponema early gains entrance to the lymph vessels and invades the blood-stream.

After the appearance of the chancre there is a "*second incubation period*" of variable length (usually six weeks to six months) during which there are no symptoms except, possibly, secondary anemia and enlargement of the regional lymph-nodes. Important changes, however, are at this time taking place. The treponemata are making good their invasion of the tissues, and the body is developing defensive reactions which lead to the presence of antibodies in the blood.

The end of this secondary incubation period is marked by the appearance of typical eruptions on the skin and mucous membranes. This has been termed the "secondary period" of syphilis. The eruption quickly disappears with treatment, but in untreated cases may persist a long time with gradual change. During this stage treponemata may be found in the blood-stream and cerebrospinal fluid, and in 80 per cent. of patients cellular changes provide evidence of cerebrospinal involvement. The other evidences of general involvement are described below.

The eruption and other symptoms of this period may be so slight as to escape notice, or may be absent altogether. Many observers think that when this is the case, the infection finally develops into the most malignant late type, but their belief is doubtless due, in part at least, to the fact that the asymptomatic type escapes treatment and consequently develops unhindered. Treatment at this time causes a disappearance of all symptoms, and if therapeutic measures are prompt, energetic, and sustained, relief is, as a rule, permanent. Occasionally the eruption may recur once or twice in the same areas, and even a "chancre redux" may appear.

During this early period syphilitic processes are no doubt also taking place in the internal organs, but they are so relatively benign at this stage as to produce very few clinical signs. For instance, the changes in the spinal fluid furnish proof that cerebrospinal involvement may take place very early in spite of the fact that other signs of such involvement cannot be found. It has been suggested that the invasion of the internal organs at this time determines somewhat the location of the later lesions. According to this view the manifestations of early (secondary) syphilis are an expression of wide-spread involvement of the entire body to which relatively little resistance is offered; the late lesions (of the tertiary stage) are, on the other hand, the result of persisting localized changes which either have renewed their activity, or by slow development have finally reached a stage in which they produce symptoms.

At the end of the secondary period, especially in patients who have been inadequately treated, there usually ensues a so-called *"latent period."* This, in turn, is followed by the *"tertiary or late period"* of visceral syphilis. The latent period may persist for only a few weeks, or for twenty or thirty years. It usually lasts for two or three years. The late manifestations which are deep seated and destructive may involve any of the organs, and often endanger the patient's life. Included among them are the nervous manifestations—paresis and tabes dorsalis.

This classical division of the course of syphilis into three stages is arbitrary and does not accord fully with our present understanding of the disease. The secondary eruption may appear while the chancre still flourishes; tertiary visceral manifestations may be produced by gummata during the period of florid secondary syphilis; and the secondary period may merge imperceptibly into the tertiary stage, or be missed entirely. Certain modern writers have therefore suggested a more rational division of the disease into two stages: early syphilis, which includes the primary lesion and the so-called "secondaries," and late or visceral syphilis. Although the dividing line between the two stages is not always sharp, certain features of each warrant the distinction. The *early stage* is characterized by the presence of a large number of treponemata in the lesions, by the prompt response to treatment, by lack of response to the administration of iodids, and by the tendency of the lesions to heal without scars. *Late* or *visceral syphilis* is characterized by the presence of a small number of organisms in the lesions, by extensive destruction of parenchyma, by the formation of gummæ and connective-tissue proliferation, by ready response to the iodids, and by the formation of scars.

Symptoms.—In the following pages syphilis will be discussed as a general continuous infection with two types of manifestations, the one occurring early and the other, as a rule, late.

Acquired Syphilis.—The *chancre* develops at the site of entrance of infection after an incubation period of from ten to sixty days, usually within about three weeks. As a rule, it is on the genital organs. It appears first as a small papule which soon erodes into a reddish ulcer often covered by a grayish-yellow exudate. This is usually somewhat elevated, but not excavated; is distinctly circumscribed; and has little or no areola of inflammation. That the often described hard or "shot-like" consistency of the chancre cannot usually be detected for one or two weeks is important to remember, as the chancre may first appear as a simple erosion without this

characteristic. The classical "*Hunterian chancre*" is deeply ulcerated with a raised (not excavated) border and a cartilaginous consistency. On the other hand, the initial lesion may never ulcerate, but remain merely a papule. Most patients have only one chancre, but about 10 per cent. have several. The lesion is most apt to be multiple when two mucous surfaces come in contact. It is rarely painful and may, consequently, pass unnoticed. If not contaminated with chancroidal infection, the chancre usually heals without treatment in four to six weeks. Phagedenic ulceration sometimes occurs in very debilitated persons, or when the lesion is both a chancre and chancroid. The chancre leaves a scar which usually persists several months. The so-called *chancre redux* is caused by organisms which remain in this scar. Extragenital chancres may appear almost anywhere on the body—the finger, lip, eyelid, tonsil, nipple, and tongue being its most frequent sites.

A chancre is always accompanied by involvement of the lymph vessels and swelling of the regional lymph-nodes which become palpable about three or four weeks after infection. They are discrete and hard. Unless the infection is mixed they do not suppurate.

General Symptoms.—While the chancre is disappearing, and during the "second incubation period," the patient experiences a few vague symptoms. There is usually moderate anemia and swelling of the general lymph-nodes. Toward the end of this period, just before the eruption, symptoms of a more pronounced nature appear, many of which are common to all bacterial invasions. The secondary anemia with pallor increases. About a third of the patients have a low-grade fever which is often intermittent. There is more or less physical and mental depression. Pains appear in the bones and joints. The patient may complain of cardiac palpitation, arhythmias, and other circulatory disturbances. As the rash appears the severity of all these symptoms increases. The fever is more constant and the temperature is, perhaps, higher; the lassitude is more noticeable; and the patient may lose weight. There is headache and pain in the bones and joints, especially at the insertions of the tendons. The spleen may or may not be palpable. Icterus is frequent, and occasionally there is recognizable enlargement of the liver. Iritis and neuritis of various nerves, particularly of the optic and auditory nerves, may occur at this time. Exaggeration of the reflexes is often noted, and rarely there may be a genuine syphilitic meningitis. This stage is said to coincide with the most wide-spread distribution of the treponema throughout the body.

The Skin and Mucous Membranes.—The eruption of syphilis is manifold in character and can simulate practically any skin disease. Certain characteristics are, however, common to all syphilitic skin manifestations: they are usually symmetrical; when papular the eruption is often arranged in circles or segments of circles, which follow the distribution of the blood-vessels; they are often polymorphic, consisting of two or more types of eruption at the same time; and unless irritated or otherwise complicated they do not cause pain or itching. There are three main types of syphilitic eruption: the macular, papular, and tubercular.

(*a*) *The Macular Eruption.*—The macular eruption or roseola ordinarily is the first to appear. It is seen usually on the abdomen and chest; the face often escapes. The rash may be nothing more than a faint diffuse blush, or may consist of clearly defined rose-colored macules of varying size.

The dilated capillaries which produce this eruption contain large numbers of treponemata, and the blood taken from a roseola spot, or the fluid which exudes from the skin on injury is highly contagious. The roseola disappears within one or two weeks. Another type of macular eruption often appears a little later, but may develop at the same time. The macule of this type is slightly elevated, persists longer than the other, is copper colored, and, in fading, often leaves a transiently pigmented spot or a faded area.

(*b*) *The Papular Eruption.*—The size of the papule varies greatly. The lesion consists of the infiltration of small areas which are at first generally distributed over the body, but later tend to become localized, particularly around the genitals and anus. In such locations the papules are inclined to become broader and to assume a wart-like character. They are then called *condylomata.* Papules may appear on the palms of the hands or the soles of the feet as slight depressions. When the scales which cover them are removed they are seen to have a reddish "coppery" color. They are indurated and tend to crack open and ulcerate. These *palmar syphilids* may develop in the late as well as in the early stages. Papules occasionally destroy the nail bed and lead to a syphilitic onychia and paronychia which is most refractory to treatment. The hair often drops out, sometimes in patches, giving a "moth-eaten" alopecia.

The most characteristic, persistent, and infectious of all syphilitic eruptions, the *mucous patch,* is papular in character. It develops on the mucous membranes of the mouth, tongue, tonsil, prepuce, and vagina as a slightly elevated, glistening, circumscribed area with a slightly depressed center. It is free from induration and is usually covered with a white or yellowish exudate. These patches often coalesce to form larger irregular areas. They may persist for months and may continue to recur for many years.

Papules occasionally suppurate and give rise to a pustular eruption. This seldom occurs early, and may be considered a more severe lesion than any of those already described. The pustules tend either to dry up and become covered with brownish-red crusts, or to break down and form large ulcers. Several varieties are described: one resembles *acne;* another *variola;* there is a third form called *impetigo syphilitica,* and a fourth, known as *ecthyma syphiliticum,* in which there is extensive suppuration and ulceration.

(*c*) *The Tubercular Eruption.*—The tuberculous or nodular syphilid often develops during an intermediary stage between early and late syphilis, its histology being more typical of the latter condition. This lesion consists of small discrete elevated nodules of a bluish-red or "ham" color, which tend to appear in circles and, spreading at the periphery, to unite and form serpiginous and other configurations. As the nodules disappear they leave an atrophic brownish area which later becomes white. In the more severe forms the nodules tend to become confluent. When they appear late in the disease they often ulcerate. They may persist many years.

True *gummata* appear in the skin and subcutaneous tissues during late syphilis. They often coalesce and ulcerate, and thus produce large areas of necrosis. The exudate from such an area dries and forms a crust; continued exudation leads to the formation of another crust, beneath this yet another, and so on until a crust of many layers appears. In addition

to the mucous patches above described other lesions may appear in the mouth, throat, or nose at any stage of the disease. The tonsils frequently, and less often the larynx, are subject to these processes. A characteristic feature of the mouth lesions is their tendency to recur and persist for many years. It is important that they be recognized because of their highly contagious character. There is no sharp dividing line between the early and the late skin lesions of syphilis. The essential difference is that the latter are more local in character, more chronic, more liable to ulcerate, and much more destructive than the early manifestations.

The Bones.—During the early stages of syphilis the patient often complains of *pains in the bones* which are due to inflammation of the bone or periosteum. The headaches and neuralgias of syphilis are often due to involvement of bone; it is possible, as the result of vascular obliteration, for necrosis and caries of the cranial bones to take place even in the early stages. It is in late syphilis, however, that the bone lesions are most apparent and most destructive. Periostitis, particularly of the long bones, is frequent. It is usually accompanied by pain, redness, and diffuse swelling. The lesion may become absorbed, but often stimulates the formation of new bone of extreme hardness, as in the characteristic *"saber-shin"* (periostitis of tibia). Exostoses are also common. *Gummata* frequently form in the bone during late syphilis. If small, they may be absorbed and leave depressions; they may cause extensive destruction of bone. Destruction of the bones of the face and nose are often the result of such gummatous processes. *Syphilitic dactylitis,* characterized by a peculiar smooth bluish swelling of the phalanges, sometimes occurs. *Involvement of the vertebræ* may lead to pain on movement, stiffness, or deformity. The pains of syphilitic bone disease are more intense at night, and are said to be often relieved by exercise.

A true *arthritis* may be an early manifestation of syphilis. This may suggest tuberculosis; or, when of an acute polyarthritic nature, rheumatic fever. In late syphilis several types of monarthritis occur. Involvement of the knee-joint which may cause the formation of a *"tumor albus"* is difficult to distinguish from tuberculosis.

The Circulatory System.—Various cardiac disturbances take place during the early stages of syphilis—tachycardia, bradycardia, and arhythmia. The heart is easily excited and quickly exhausted. Probably two-thirds of the patients with early syphilis show these so-called functional cardiac disturbances. It is questionable how often this condition represents a true myocarditis. Undoubtedly early syphilitic myocarditis does occur, but it is rare. The systolic murmur which is often heard can be ascribed, as a rule, to the anemia. Involvement of the cardiac nerves, the vagus and the sympathetic, as well as psychic influences probably play a rôle in the production of these disturbances.

Later in the disease, gummata and interstitial inflammatory changes occur in the heart, but there is considerable divergence of opinion as to their frequency. Warthin believes that syphilis is by far the most frequent cause of myocardial disease and ascribes to the treponema even the very common myocardial fibrosis; but this is perhaps an extreme view. A gumma of the bundle of His is the most common cause of the Stokes-Adams syndrome; and may cause sudden death. Fibrous replacement of the myocardium may be the extension of a process beginning in the cor-

onary arteries. The symptoms are the same as those of myocardial disease from other causes. Frequently there are evidences of myocardial failure, and sometimes pain over the precordium suggestive of angina. Cardiac aneurysms sometimes develop in the scar of a healed gumma. Distortion of the aortic valves leading to cardiac insufficiency is often seen in this disease and represents an extension to the valves of syphilitic aortitis.

Syphilis has been described as primarily a disease of the blood-vessels. Obliterative endarteritis in which all coats of the artery are involved occurs commonly in the smaller vessels of every part of the body. Small gummata are sometimes located in the walls of the vessel, particularly in those of the cerebral vessels. Syphilitic aortitis, which is often limited to the thorax and usually begins near the root of the vessel, is a very common lesion. The adventitia and media are first involved with obliteration of the *vasa vasorum;* the intima then becomes thickened and is covered in spots with a hyaline fibrinous coat. For a long time there may be no symptoms; then dyspnea and pain appear, the dyspnea first. The pain, which may be constant or intermittent, tends to increase progressively in severity. It is usually located beneath the sternum and may radiate in any direction. Various murmurs are heard and at times a faint pericardial friction sound. When the process extends to the aortic ring and valves, serious consequences ensue, which lead eventually to death. Aortitis often leads to aneurysm.

The Respiratory Organs.—In early syphilis mild disturbances in the upper air passages are frequent and cause hoarseness and coughing. Later, deeper and more destructive processes occur. Single gummata, or, more frequently, diffuse gummatous infiltrations, develop and often break down into deep-seated ulcers. Hoarseness and aphonia commonly result. Such syphilitic processes can, as a rule, be distinguished from tuberculosis by the relative paucity of subjective signs. There is most danger when the epiglottis and larynx are involved, for edema and inflammatory swelling may cause complete closure and death from suffocation. Ulceration may destroy the laryngeal cartilages.

Syphilis of the lung has long been considered a rare disease, but evidence is now accumulating which shows that it is more frequent than has been generally supposed. Cough with expectoration (sometimes bloody), loss of weight, and a variable fever—symptoms which are identical with those of pulmonary tuberculosis—are the usual manifestations. The physical signs, except perhaps for their location, also suggest phthisis. Early in the luetic process, radiographs of the lungs may show shadows the size of a 25-cent piece some distance from the hilum shadow. At this time there is no increase in the markings of the lung or in the hilum shadow. Later, as the disease progresses, the infiltration becomes more wide-spread and may perhaps be recognized by the fact that it is largely limited to one part of one lung, usually the middle or lower portion. When these signs fail, recourse must be had to the Wassermann reaction or to the therapeutic test. With proper treatment the prognosis is excellent.

The Digestive Organs.—(*a*) *The Esophagus.*—Syphilis of the esophagus is rare and usually represents extension of the infection from some neighboring structure.

(*b*) *The Stomach.*—Syphilis of the stomach is more frequent than was formerly thought. Early in the disease functional gastric disturbances are

frequent. The patient complains of lack of appetite and of a sense of pressure in the epigastrium. At times there is regurgitation of food. A large percentage of patients have lowered acidity, perhaps anacidity or achylia. Little is known of the actual gastric pathology at this stage and it has been suggested that much of the distress and disturbance of function is due to disease of the vagus nerve. The known syphilitic diseases of the stomach wall are usually late manifestations. There may be ulcer, tumor, or stenosis. Ulcer, which may occur relatively early, is due to gumma or to an obliterative endarteritis. The symptoms are those of any ulcer except that in syphilis there is apt to be lowered acidity. Syphilitic gastric tumors result from the formation of gummata or from fibrous thickening of the submucosa and muscularis. This latter process may cause contraction of a large part of the stomach wall or may attack chiefly the region of the pylorus, and cause pyloric stenosis. Stenosis at the pylorus can also be caused by the strictures which result from broken-down gummata.

The symptoms of syphilis of the stomach are variable and not characteristic. Abdominal pain and distress, vomiting, gastric anacidity, blood in the gastric contents and feces, and emaciation are all symptoms of gastric syphilis as well as of other diseases. It is very difficult to distinguish a syphilitic tumor or thickening from cancer. A palpable tumor of the stomach which does not cause stenosis, and is accompanied by disturbance in several other abdominal organs, and by gastric pain which occurs chiefly at night, should suggest syphilis. In distinguishing syphilis from carcinoma of the stomach roentgenology is usually of little aid. In both conditions there is the same filling defect; but in syphilis the emptying time may be abnormally short, while in cancer it is usually lengthened. Even exploratory laparotomy often leaves the surgeon in doubt. For final diagnosis it is usually necessary to rely upon the Wassermann reaction and the results of antisyphilitic therapy. The author has seen 2 cases of what appeared to be inoperable cancer of the stomach cured by antisyphilitic treatment.

(*c*) *The Intestines.*—Syphilis of the intestines is rare. In early syphilis a diarrhea occasionally occurs which if untreated may become chronic. This symptom is encountered more frequently, however, in the later stages of the disease. Such catarrhal diarrhea is particularly severe in cachectic individuals. Gummata occasionally form in the intestinal wall; they may break down into ulcers which in healing produce circular scars and stenosis. Syphilis of the intestine may, in its clinical aspects, resemble tuberculous enteritis or carcinoma. The concomitant presence of tumor, bloody diarrhea, and stenosis, while by no means characteristic, should suggest syphilis. Gummata of the rectum above the sphincter are relatively frequent. They tend to break down and ulcerate with the eventual formation of strictures. Fistulæ and strictures of the rectum and anus are common manifestations of late syphilis.

(*d*) *The Liver.*—Invasion of the liver is frequent, and symptoms referable to this organ are encountered often, both early and late. The mild icterus suggestive of catarrhal jaundice which occasionally appears either before or during the efflorescence may be an extension of the disease from the duodenum or a true exanthem of the bile passages. In early syphilis, true hepatitis sometimes appears with enlargement and tenderness of the liver, enlargement of the spleen, and fever. A rapidly fatal disease

of the liver, said to be identical with *acute yellow atrophy*, may develop within a year after infection. Jaundice, vomiting, great prostration, delirium, and eventually coma are symptoms. It has been suggested that poorly treated syphilis is a potent cause of acute yellow atrophy of the liver, but the occasional destructive influence of mercury and arsenic upon the hepatic parenchyma must always be considered.

The late manifestations of syphilis of the liver are the formation of gummata and chronic interstitial inflammation, either alone or together. Gummata may be miliary (often multiple) or they may reach the size of large tumors. They usually begin in the immediate neighborhood of a blood-vessel, which they eventually destroy. Fibrous tissue with scars usually results, but other retrogressive changes may lead to localized fatty or amyloid degeneration. As a rule, gummata of the liver do not break down, but when they do, an irregular perplexing fever often ensues.

Chronic interstitial hepatitis begins with a cellular infiltration around the blood-vessels which extends and leads finally to the production of thick fibrous tissue. Gradually there develops a cirrhosis of the liver in which the parenchyma is replaced by this newly formed connective tissue. Bands of tissue often divide and distort the liver so that it assumes an abnormal, often bizzare shape, which serves to distinguish this form of cirrhosis from the ordinary type described by Laennec. At the same time gummata may be present. This type of cirrhosis develops slowly over a period of years. It may exist for a long time without producing symptoms, though, as a rule, definite signs are present. The liver is often nodular. It may be larger than normal or, because of the constricting bands, may undergo atrophy in one part and hypertrophy in another. Ascites, hematemesis, and other signs of portal obstruction are evident. Jaundice and albuminuria are usually present, as well as severe pain and a low-grade fever. With gummata alone, the prognosis is relatively good, but with chronic interstitial inflammatory changes, treatment avails little.

(*e*) *The Pancreas.*—Indurative pancreatitis occasionally occurs as a late syphilitic process. The parenchyma is replaced by connective tissue and the organ becomes hard, usually larger than normal, and in thin individuals can occasionally be palpated. This type of interstitial pancreatitis is, however, rarely recognized during life. Gummata also occur. Syphilis of the pancreas is often associated with syphilis of the liver. Syphilitic *diabetes mellitus* is occasionally reported, but when subjected to critical tests, including not only the Wassermann reaction but also the therapeutic test as well, is found to rest very infrequently upon a purely syphilitic basis. Joslin reports that 16 out of 1000 diabetics gave a positive Wassermann reaction; this is a very small proportion, and even among these few patients it is not known how frequently syphilis was the real etiological agent.

The Kidneys and Urinary Tract.—Mild albuminuria, with or without casts, is a frequent accompaniment of early syphilis, and is usually associated with no other symptoms of renal involvement. During this period there may develop, however, a true acute syphilitic nephritis with edema and other symptoms identical with those of the usual form of acute nephritis. The treponema and not mercury or arsenic, as is sometimes suggested, is probably the causative agent. A little later there occasionally appears a subacute inflammatory or degenerative disease of the kidney to which the term "nephrosis" has been applied. Its onset may be rapid or insidious. The

disturbance is distinguished by marked edema, pallor, prostration, headaches, and scanty excretion of urine containing much albumin, and a sediment composed in part of degenerated kidney epithelium, hyaline and granular casts, and certain characteristic lipoid bodies. These lipoid bodies appear in the urinary sediment as small droplets which, when viewed in a polarized light, seem to be divided by a black cross into four highly refractile sections. They serve to distinguish this disease from nephritis of a similar character which occasionally follows the excessive use of mercury. The prognosis is good under treatment, but when untreated this process causes uremia, or it may change gradually into a chronic intestinal nephritis.

In its later stages, syphilis sometimes gives rise to a chronic interstitial nephritis, which may follow the disease just described or develop gradually without previous symptoms. The syphilitic etiology of this form of interstitial nephritis, when it is typical, may be recognized by the following distinctive characteristics: there is often no elevation of blood-pressure; polyuria is usually absent; the water concentration test shows little impairment of the ability of the kidneys to excrete nitrogen and salts; and there is moderate albuminuria with an abundance of hyaline casts and occasionally lipoid bodies. With treatment, the outlook for arresting the disease is good.

Gummata occasionally appear in the kidneys, but cannot be recognized during life unless they reach the size of great tumors.

The urinary bladder sometimes gives trouble in early syphilis. It presents the symptoms and cystoscopic appearance of chronic cystitis or tuberculous cystitis. In late syphilis ulcers may appear as the result of broken-down gummata.

The Testicles and Ovaries.—Animal experiments have shown that the treponema grows with especial ease in the testicle, a fact corroborated by clinical experience. The semen in early syphilis may contain treponemata, even when there is no clinical evidence of testicular involvement. Orchitis, a fairly frequent and characteristic manifestation of syphilis, may occur early, although it appears, as a rule, two or three years after primary infection. It is usually double. The testicle is swollen, hard, and rarely painful. The epididymis is involved in only about half the cases. This chronic interstitial inflammatory process may destroy the parenchyma and produce finally a small sclerosed testicle, but only certain parts of the organ may be involved and some parenchyma left to function. Syphilitic orchitis may be confused with gonorrhea, tuberculosis, or carcinoma. Pain, fever, and involvement of the epididymis are characteristic of *gonorrhea;* pain, degenerative changes, and the presence of *tubercle bacilli* in the urine characterize *tuberculosis;* while *carcinoma* grows faster, is usually unilateral, and has an even contour. Gummata with the eventual formation of fistulæ occasionally involve the testicle.

Little is known of syphilis of the ovary. It probably leads to menstrual disturbances and eventually to amenorrhea and sterility.

Other Organs of Internal Secretion.—The *thyroid gland* is occasionally enlarged in early syphilis, most often when untreated. Late in the disease it may undergo a chronic inflammatory change which results in fibrosis and may cause symptoms of pressure or lead, perhaps, to myxedema.

Syphilitic involvement of the *hypophysis* and its neighboring tissues

can give rise to *diabetes insipidus* or to the endocrine disturbance known as *distrophy adiposogenitalis*. Syphilis may destroy the *adrenals* and induce Addison's disease.

The Nervous System.—Syphilis of the central nervous system is difficult to classify because from neither an anatomical nor clinical standpoint are the several types clearly defined. They occur together, overlap, and merge into one another. For purposes of description the following grouping is the best:

1. Meningeal syphilis.
2. Cerebrospinal syphilis:
   (*a*) Vascular.
   (*b*) Parenchymatous.

1. The *meninges* are involved early and with great constancy. Estimates as to the frequency of such disturbances in early syphilis, which are based upon examination of the spinal fluid, vary from 50 to 100 per cent. Dreyfus found changes in the spinal fluid of 80 per cent. of patients with syphilis. The vast majority of such patients give no clinical evidence of meningitis, yet the character of the cells in the lumbar fluid shows that a true meningitis, though of low degree, exists. The spinal fluid undergoes some elevation of pressure, a pleocytosis, chiefly of mononuclear cells with occasional polynuclear and plasma cells, and the globulin content is markedly increased. The Wassermann reaction of the spinal fluid may be negative at this stage, although that of the blood is positive. These signs of meningeal involvement disappear quickly if treatment is thorough, but they may remain for a long time in poorly treated or neglected patients. Their chief importance lies in the fact that if they are disregarded, a small percentage of the subjects will, years later, develop tabes or general paresis.

Less often there occurs a syphilitic meningitis with outspoken clinical signs. This type may appear very early, even before any other general manifestations are evident, but it usually develops simultaneously with the skin symptoms during the first generalized invasion of treponemata. There is manifest inflammation of the meninges with connective-tissue proliferation and the formation of new granulation tissue which dips into the brain substance and thus establishes a true meningo-encephalitis. As usual, there is involvement of the smaller arteries and veins. The meningeal lesions are not evenly distributed, but are confined to more or less restricted areas. Basal meningitis, which involves chiefly the region of the optic chiasma and the space between the peduncles, is the most frequent form. The coverings of the cord are often involved in the region of the posterior columns (tabes). The symptoms depend largely upon the location of the inflammatory process. The preponderance of basal meningitis accounts for the frequency of syphilitic paralysis of the cranial nerves. Involvement of the region of the hypophysis may lead to *diabetes insipidus*. If the cortex is attacked, psychic disturbances, headaches, vomiting, aphasia, and perhaps Jacksonian epilepsy may follow. There may be delirium, coma, or convulsions. The onset of epilepsy in a patient of thirty or more years of age is always suggestive of cerebral syphilis. With energetic treatment the prognosis of early syphilitic meningitis is good.

Syphilis of the dura mater is usually an extension of the disease from the other membranes, or from the bone. Two types have been distinguished,

a *pachymeningitis hæmorrhagica interna* and a *pachymeningitis hypertrophica*. Both are serious.

2. *The Brain and Cord.*—Syphilis of the brain most often appears as part of a syphilitic meningitis—meningo-encephalitis. *Involvement of the blood-vessels*, as repeatedly stated, is a prominent feature in all syphilitic pathology, especially here, for it is most often through the vessels and the accompanying perivascular infiltration that the disease is spread to the brain. The changes are essentially interstitial and affect the nervous tissue only indirectly. At the same time treponemata may penetrate into the brain substance and, on reaching the nerves themselves, give rise to a true parenchymatous cerebrospinal syphilis. Luetic *endarteritis obliterans* often interferes with the cerebral circulation and leads to softening of the brain. These processes seem to have a preference for the interpeduncular space at the base of the brain and for certain cortical areas. Both may be involved. With involvement of the base, disturbance of the cranial nerves is frequent. The optic nerve, the extrinsic nerves of the eye, and the auditory nerve are most often affected. It is said that an optic neuritis is much more common in early syphilis than is ordinarily thought. With syphilis of the cortex there may be headache, psychic disturbances, Jacksonian epilepsy, and various motor symptoms. While the several forms of cerebrospinal syphilis just described usually occur early in the disease, often in the first year, they may also appear late. As a rule, however, the late manifestations of this type are due to gummata or, usually, to combined gummatous and fibrous processes which arise in the meninges, and extend along the vessels to brain or cord. The symptoms depend upon the location of the tumor.

The prognosis of these interstitial processes is good if treatment is early and energetic. This is not true, however, when the treponema has extensively invaded the brain substance and is not within easy reach of mercury and arsenic. When the treponema invades the nerves themselves, degeneration of these structures follows and irreparable damage is done.

If such invasion is extensive it must be called *parenchymatous cerebrospinal syphilis*. Outstanding examples of this group are paresis and tabes dorsalis. The symptoms of the parenchymatous form are similar to those of the meningeal and vascular forms, but vary, of course, according to the location of the process. There are three features which are said to characterize the symptoms of cerebrospinal syphilis: (*a*) their extreme variability and disappearance with recurrence at short intervals; (*b*) their multiplicity and involvement of widely separate areas; and (*c*) their association with structures at the base of the brain.

Since Noguchi demonstrated the presence of the treponema in the brain of paretics, paresis and tabes dorsalis are no longer called parasyphilitic diseases, but are regarded as true manifestations of active syphilis. They are placed in a category of their own because, being a late effect of the localization of the organism in the parenchyma of the brain or cord, each presents a fairly well-defined symptom complex and can be regarded as a definite clinical entity.

The Eye and the Ear.—The eye is frequently involved in syphilis and sometimes offers the only recognizable symptom. A plastic *iritis* often occurs early, and *iridocyclitis* perhaps a little later. An especially severe form of iritis, the iritis papulosa, may appear relatively early or as a late

manifestation. Retinitis develops in late syphilis; the retinal vessels show characteristic changes, and hemorrhages may occur. The optic nerve is not infrequently congested in early syphilis, while in the later there is often an optic neuritis or neuroretinitis which if untreated may lead to optic atrophy. Reference has already been made to the frequency with which one or more of the extrinsic eye muscles becomes paralyzed as the result of nerve involvement.

Otitis media is often an early manifestation of syphilis. It differs but little from other forms of otitis media except in the unusually rapid loss of hearing, the pains in the bone, and the fact that the disease is usually bilateral. In late syphilis the process may lead to destruction of the internal ear. Deafness follows involvement of the auditory nerve.

Other Indefinite Late Manifestations.—Certain other indefinite symptoms of a general nature are prone to occur in late syphilis. A low-grade fever, otherwise difficult to explain, should always excite a suspicion of syphilis. The fever of pneumonia and of typhoid fever has been known to continue long after apparent recovery, and then promptly subside as soon as a positive Wassermann reaction was discovered and antisyphilitic treatment instituted. The emotional instability which we call neurasthenia occasionally occurs in late syphilis without other signs of disease. An indefinite state of ill health with malaise, anemia, and lack of initiative may also be the result of so-called latent syphilis.

Congenital syphilis is transmitted only through the mother. If the disease originally comes from the father, he infects the mother, and she, through the placenta, infects her offspring. The often quoted law of Colles that a healthy mother who gives birth to a syphilitic child becomes immune to the disease, and the converse law of Profeta, that the healthy child of a syphilitic mother acquires immunity, are now both known to be false. The blood of the apparently healthy mother or infant gives a positive Wassermann reaction which demonstrates the presence of latent or, more properly, asymptomatic syphilis. The duration of the infection in the parent has an important influence upon the likelihood of transmission. Fournier has shown that the disease is transmitted usually during the first three years after infection. The danger then gradually lessens, so that five to ten years after the initial lesion syphilis is, as a rule, no longer transferable by the father. The mother, however, may even after twenty years infect her child.

If the fetus is infected early in the disease of the parent it usually dies *in utero* and a miscarriage results. After a time, perhaps after two or more such miscarriages, there may be born at full term a child with unmistakable signs of syphilis, who dies during the first year of life. Still later the mother may give birth to an apparently healthy child who displays a positive Wassermann reaction and subsequently shows other evidence of the disease. These children are often frail, anemic, undersized, marasmic, and retarded in development. They are likely to succumb early to various intercurrent diseases. Occasionally the child with congenital syphilis shows no signs of the disease until after ten or twelve years, or even longer, when severe late manifestations may appear. The tissues of the child born with manifest syphilis harbor the treponema in enormous numbers. The invasion is greatest in the liver and adrenals, and next in the lungs.

The symptomatology of congenital syphilis does not differ materially

from that of the acquired disease except that there is no primary sore and the late manifestations appear much earlier, sometimes, indeed, simultaneously with the usual early symptoms. Those children, who at birth show outspoken evidence of syphilis, and who usually die within the first few weeks of life have a true treponema septicemia. This is manifested by the bullous eruption on the skin; the fissures about the angles of the mouth and nose; the characteristic nasal discharge, to which the name "*snuffles*" has been given; the enlargement of the spleen and liver; the bony changes about the joints; the poor state of nutrition; and the faulty development. The congenitally syphilitic children who are conceived at a later period of the parental disease, and who at first show no recognizable symptoms, a little later usually appear unmistakably syphilitic. *Snuffles* is one of the most constant symptoms. *Eruptions*, macular or papular, appear upon the skin, most often on the buttocks or the face; the macules are a coppery brown color with well-defined edges. Instead of this type of rash there may be a mere erythema or an eczema. The papules tend to become confluent and to cover large areas, especially on the hands and feet and around the mouth. In the severe cases bullæ appear, which burst and may produce large sores. The skin and mucous membranes of the lips may undergo a peculiar diffuse infiltration, called "*cheilitis diffusa*." At the corners of the mouth fissures appear; when these are deep and ulcerated they are called *rhagades*. In healing they leave linear radiating scars which are peculiarly characteristic of congenital syphilis. Syphilitic *onychia* is common, and the hair may fall out. These children are apt to be unusually restless at night, and are said to have a peculiar, harsh high-pitched cry.

Teeth.—Hutchinson's teeth provide the most characteristic feature of congenital syphilis. The central incisors of the permanent teeth, most often the upper, are notched on their free borders as if a half-moon-shaped piece had been chipped out; moreover, they are usually peg shaped; that is, smaller at the free end than at the gums. Additional defects involving peculiarities of form, size, and spacing of the teeth are seen, but these last are common to other states of malnutrition and are not peculiar to syphilis.

Circulation.—A hemorrhagic diathesis has been described as an expression of congenital syphilis, but it is probable that this is identical with that seen in other forms of sepsis.

The Digestive Organs.—The liver is often extensively involved and is usually enlarged. It is subject to the same lesions observed in acquired syphilis. *Diffuse hepatitis* may develop about the time of puberty and lead to cirrhosis of the liver. The *spleen* also is often enlarged. Both the *pancreas* and the *kidneys* are subject to chronic interstitial inflammation in late congenital syphilis and both may be retarded in their development.

Bones.—Characteristic of congenital syphilis is an *osteochondritis* which attacks the centers of ossification between the shaft and epiphysis of the long bones. The normally thin zone of calcification becomes very much widened and irregular, a condition easily recognized in the radiogram. Swelling and pain in this area are the chief symptoms. The lower end of the femur is the region most often attacked.

The Nervous System.—In congenital syphilis the central nervous system is subject to the same changes noted in the acquired form. In addition, the retarded and abnormal cerebral development may lead to epilepsy, hydrocephalus, or idiocy. Even juvenile paresis and tabes may occur.

The fontanels remain wide, and when the child cries the veins of the head may become greatly dilated.

The Eye and the Ear.—Later in the disease, often in adult life, there is an *inflammation of the cornea,* and interstitial keratitis, which is seldom seen in the acquired disease, but is especially characteristic of congenital syphilis. If untreated it leads to cloudiness of the cornea and later perhaps to blindness. Both eyes are often attacked. *Optic neuritis* is also common, but is more apt to occur during the first three months of life. Involvement of the ear is common, and may cause complete deafness.

A triad of signs was described by Jonathan Hutchinson as especially characteristic of congenital syphilis; all have been mentioned above: (*a*) "Hutchinson's teeth," (*b*) interstitial keratitis, and (*c*) deafness.

Diagnosis.—The history of the patient is always of diagnostic importance, particularly when it points to a primary sore or secondary rash. In women the history of repeated miscarriages is significant. Search should always be made for the scar of a chancre. It should be borne in mind that the primary lesion is often overlooked or forgotten, and that, indeed, it may never have been present. Persistent enlargement of the lymph-nodes, particularly of the epitrochlears, and scars of old skin lesions, should be regarded as significant. Nodes on the bones, particularly the characteristic "saber-shins," are also noteworthy. Hutchinson's triad in congenital syphilis, the characteristic teeth, keratitis, and deafness, should be remembered in determining diagnosis. When there is a suspicious primary sore a search for the treponemata should be made with the dark-field. On a properly prepared film they are usually not difficult to find.

The Wassermann Reaction.—The most important factor in the diagnosis of syphilis is the Wassermann reaction. A positive reaction tells of the presence in the blood or spinal fluid of certain defensive bodies which have developed as a result of the invasion of treponemata. For the development of a positive reaction a certain incubation period is required, although rarely the test may be positive as soon as the primary sore is recognizable. More often, however, the result is not immediately positive; it cannot be obtained until about the time the so-called secondary symptoms develop, usually during the eighth or ninth week after infection. A positive Wassermann reaction is the most constant of all of the signs of syphilis, and in the vast majority of cases it remains positive until influenced by treatment. With the rarest exceptions, a positive Wassermann reaction is always indicative of active syphilis—active even though it may not produce symptoms. Much, however, depends upon reliability of technic, for technical errors are a fruitful source of trouble. "*Wassermann fast*" is the term which has been applied to the blood of those patients whose Wassermann reaction, in spite of prolonged and persistent treatment, remains positive. These patients probably have deep-seated lesions which are difficult to reach; specific treatment in such cases should be continued indefinitely.*

Luetin Reaction.—The luetin reaction as devised by Noguchi is an anaphylactic phenomenon analogous to the tuberculin reaction which the syphilitic person may exhibit when an extract of treponemata is injected intracutaneously. It is said to be of value chiefly in the late stages. It gives a false reaction when the patient has been taking iodids, and is not sufficiently reliable to warrant diagnostic dependence.

*The Kahn precipitation test is almost as reliable as the Wassermann reaction, and in some laboratories has supplanted it. Its great advantage is the simplicity of technic.

Spinal Fluid.—An examination of the spinal fluid is advisable, and no patient who has had syphilis should be discharged as cured until this has been done. The presence of a positive Wassermann reaction in this fluid indicates active cerebrospinal syphilis, and if the reaction remains positive long, the patient is fortunate if he escapes paresis or tabes. Another constant accompaniment of syphilis of the central nervous system is an increase in the globulin content and cell count of the spinal fluid. A *positive globulin test* and a *mononuclear cell count* of more than 8 or 10 per cubic millimeter is always suggestive of syphilis. In spinal fluid the *colloidal gold reaction* gives curves which are characteristic of the several syphilitic diseases of the central nervous system.

Prognosis.—Syphilis can be cured. Much depends, however, upon the promptness with which treatment is instituted and the energy and persistence with which it is carried out. The ease with which cure can be accomplished is in inverse ratio to the age of the infection. If begun within the first few weeks or months after infection, sustained treatment usually means an early and assured cure. After two or three years cure is more difficult, while in those cases of ten or twenty years' duration complete eradication of the infection is extremely difficult and often impossible. The lesions of early syphilis usually heal without causing loss of function, but in late syphilis with deep-seated lesions and extensive destruction of parenchyma there can never be complete restoration of function. Chronic syphilis is refractory to treatment because of the persistence of pathological processes beyond the reach of medication. For the same reason congenital syphilis does not yield readily to therapeutic measures.

Prophylaxis.—The best way to escape syphilis is to avoid exposure. Immediately after exposure the disease can generally be prevented by the prompt and thorough application of calomel ointment to the contaminated parts (calomel, 3 parts; lanolin, 1 part; benzoinated lard, 2 parts). It should be emphasized that this application, to be effective, must be made promptly, preferably within two or three hours, certainly within six or eight hours, after exposure.

Treatment.—General.—The patient himself, as well as the disease, requires treatment. If he has fever, he should be kept in bed, and other symptoms of a general or specific nature must be combated with appropriate remedies. Great attention should be paid to hygiene. Alcohol should be avoided, worry and overwork prevented as far as possible, and sufficient sleep and recreation specifically prescribed. A simple, rational diet should be ordered, because intestinal disturbances often accompany the taking of mercury. For the same reason careful attention should be paid to the hygiene of the mouth, and the teeth should receive the best of care. Repeated examinations of the urine and frequent physical examinations should be made. Every patient, no matter what the circumstances, should in the beginning be told of the nature of his infection and should be warned of the tediousness of successful treatment. Otherwise the necessity for treatment will not be sufficiently appreciated and failure may result. If the patient is married, the wife or husband, as the case may be, must be informed of the situation, and due precautions taken to prevent transmission of the disease.

Specific.—Attempts have been made to abort syphilis by excising the primary sore, but have always failed, because when this lesion is recognized

the treponemata have already invaded the neighboring lymph-glands in large numbers, and thence have access to the general circulation. Abortive treatment, however, may be successful when proper medication is promptly instituted. If the therapeutic measures described below are immediately begun and consistently employed, the progress of the disease can often be stopped at the earliest stage and further manifestations prevented.

For this reason one should always examine by the darkfield or India ink method the fluid which exudes from any suspicious sore, and if the treponema is found, treatment should be started without waiting for the development of a positive Wassermann reaction or the appearance of other symptoms. When treatment is begun promptly a comparatively short course of medication suffices to bring about a cure. The longer treatment is delayed, the more difficult it becomes to achieve a complete recovery.

To be effective, treatment must be sustained and carried out according to some definite plan. Desultory treatment permits the treponema to gain a stronger foothold and to become refractory to treatment. Three drugs are of value in the treatment of syphilis—mercury, arsphenamin, and the iodids. The first two are actively treponemacidal, and should be administered during all stages of the disease. The iodids aid in the resorption and removal of the late manifestations of syphilis and should, therefore, be used chiefly in the late stages.

Mercury is effective in proportion to the quantity introduced into the circulation. *Administration by mouth* is the easiest and commonest method, but the least effective, because a large part of the mercury often passes unabsorbed through the bowel. It is also objectionable because the griping and diarrhea which it excites frequently prevent its administration in sufficient amounts. Its advantages are its ease of administration and secrecy. Metallic mercury (blue pills), calomel ($\frac{1}{4}$ to $\frac{1}{2}$ grain), the bichlorid (1/40 to 1/20 grain), and the protiodid ($\frac{1}{6}$ to $\frac{1}{4}$ grain) are the forms in which mercury is usually given by mouth.

The administration of mercury by injection is the method commonly used by specialists today. A few years ago the intramuscular injection of some insoluble salt in suspension, usually the salicylate, was in vogue. The *salicylate* when absorbed is an effective treponemacide, but its administration possesses certain marked disadvantages. The injection itself is often painful; the drug may produce severe local reactions, and if it is thrown directly into a vein, pulmonary embolism may result. Its chief disadvantage, however, lies in the uncertainty of its absorption. A single dose may require weeks for absorption. There is no way of stopping absorption after the drug has been given—a state of affairs which in the event of salivation may lead to serious results. A 10 per cent. emulsion of mercury salicylate in oil is commonly used. This can be obtained in sterile ampules. It is advisable to administer $\frac{1}{2}$ grain as the first dose, and thereafter 1 grain every four to seven days.

The most satisfactory method of injecting mercury and that most commonly used today is the intravenous administration of some soluble salt. It has the double advantage of accuracy of dosage and ease of control. Its disadvantages are the dangers which surround all intravenous medication, especially if carelessly done, and the fact that the injection must take place daily. Nevertheless, in the hands of physicians who are

treating large numbers of syphilitics, it has proved to be the best method of administering mercury. Various soluble salts of mercury have been injected. The *bichlorid* has been largely discarded because of its irritating local effect. The *oxycyanid* or the *cyanid* (1 per cent. solution in distilled water) is better. At first 1/15 grain should be given daily, and the dose should gradually be increased to 1/5 grain. Asepsis is essential.

For the great number of patients who cannot go daily to the physician *inunction* is by far the best method of administering mercury. It is of advantage, because mercury is readily absorbed through the skin and because clinical experience has shown such treatment to be efficacious. Its disadvantages are the color of the ointment and the fact that its administration cannot be kept secret. The official *unguentum hydrargyri* or *"blue ointment"* should be used ($\frac{1}{4}$ to 1 dram rubbed in daily). Its absorption is facilitated if just before beginning the inunction the patient takes a hot bath. The rubbing should continue fifteen or twenty minutes until practically all of the mercury has been taken up. Different areas of the body should be treated in succession (chest, abdomen, back, inner aspect of the thighs, etc.). The inunctions sometimes produce an erythema or an eczema which disappears when the drug is discontinued. Occasionally stomatitis also appears as an indication for stopping treatment, but this occurs much less frequently when the mouth receives proper hygienic care.

Arsphenamin is a powerful treponemacide and, in most cases, causes a rapid disappearance of syphilitic manifestations. Under its influence a florid roseola or a macular eruption disappears almost like magic. For the final cure of syphilis, however, and the removal of all foci of infection it probably possesses no advantages over mercury. The two should be used together. Arsphenamin is administered intravenously. It deteriorates rapidly when exposed to the air, and each ampule should, therefore, be examined for leaks before use. Only freshly distilled water is to be employed for preparing the solution and neutralization of the dissolved salt should be exact. The drug should be administered in sufficient dilution within a few minutes after preparation. It should be introduced slowly, with absolute asepsis. If these precautions are observed, many of the so-called by-effects of arsphenamin will be avoided. The dose is 0.2 to 0.6 gm. The salt, first dissolved and neutralized, is diluted with 100 to 150 c.c. of freshly distilled water and injected by the gravity method into a superficial vein at the elbow. When the veins of the arm are not within easy reach the external jugular vein is sometimes used. If the needle is inserted properly in the vein there is no pain or discomfort. If not, there is an intense burning at the site of injection and the operation must be temporarily discontinued, as the subcutaneous injection of the drug causes great pain and ultimate necrosis of tissue. In the hands of experienced men, administration of arsphenamin with a syringe is often satisfactory. This drug has been placed on the market in a neutralized and diluted form, sealed in glass containers, and ready for administration. Such preparations are said to be safe and effective. In administering arsphenamin such evidences of *hypersusceptibility* as dyspnea, cyanosis, or collapse should be watched for. These are signs for immediate discontinuance of the injection. The drug sometimes excites a reaction when given during an intercurrent disease. If albuminuria and other symptoms of nephritis appear during a course of arsphenamin, treatment should be temporarily discon-

tinued. Arsphenamin should be given cautiously when there is syphilis of the eye, especially of the optic nerve. It should not be given in syphilis of the liver. In chronic cases of latent syphilis arsphenamin treatment should not be started too energetically.

Neo-arsphenamin is a modified form of the drug preferred by some because of its greater ease of preparation, but it is somewhat less effective, and for this reason is not as generally used as the original preparation.

A *silver salt of arsphenamin* is highly recommended in some quarters as having greater treponemacidal powers, but it has not yet come into general use, and any judgment as to its value must be withheld. It is given in somewhat smaller doses (0.1 to 0.3 gm.) than arsphenamin and can be used without previous neutralization. Sulpharsphenamin also has been highly recommended.

Tryparsamid, a recently devised salt of arsenic, seems to penetrate structures of the central nervous system more readily than does arsphenamin. Reports indicate that it is of value particularly in meningovascular neurosyphilis and in early paresis and tabes. It is of little help in advanced paresis and in syphilis elsewhere. The usual adult dose is 3 gm. given intravenously at weekly intervals. It should be used cautiously and only under careful ophthalmologic control, as it may cause permanent visual impairment or blindness.

Plan of Treatment.—The method and routine by which these various antiluetic agents are administered is determined by the bias of the physician. All agree that the treatment should be energetic. Fournier devised a form of intermittent treatment which holds good today. Mercury and arsphenamin are usually given in "courses" with appropriate intermissions. Some, following Fordyce, give the two drugs simultaneously; others, in alternate periods. When a particularly intensive treatment is desired the former method can be used, but in the treatment of visceral syphilis the alternating plan is usually preferable. The first dose of arsphenamin should be small (0.2 or 0.3 gm. for an adult). After this the full dose of 0.4 to 0.6 gm., according to the sex and size of the individual, should be given. A *course* consists of six doses given at intervals of five to seven days. After an interval of one week mercurial inunctions should be given for six weeks; then, after another interval of one or two weeks, a second course of arsphenamin should be instituted. Three or more such courses with each drug should be given, and followed by a respite of one month. The Wassermann test should then be made on the blood, and if the reaction is still positive, treatment continued. If the reaction is negative, the test should be repeated at intervals of three months for a year. Should it again become positive, treatment must be resumed. This routine may be varied according to the nature and age of the infection. Early cases are usually controlled by a relatively short course of treatment; late cases require more.

Potassium (or *sodium*) *iodid* should be given in all except the very earliest infections. Even in these there is no objection to its use. In cases of old visceral syphilis a preliminary, rather intensive treatment with iodids for one or two weeks renders subsequent medication more effective. During arsphenamin and mercury treatment iodids should be administered by mouth in progressively increasing doses of 10 to 40 grains three times daily. Even larger amounts are sometimes given. The intravenous injec-

tion of such a readily absorbable drug as potassium iodid is unnecessary and not without danger.

The treatment of *congenital syphilis* differs but little from that of the acquired form. Babies should be given mercury by spreading the ointment upon the abdominal binder, or by mouth in the form of gray powder ($\frac{1}{2}$ grain three times daily). Potassium iodid is of value especially for the deeper lesions. It may be given in the form of Gilbert's syrup, which contains both mercury and potassium iodid (5 to 15 drops three times daily according to the age of the child). Arsphenamin is also of value and may be injected into one of the veins of the neck. Children should receive intermittent courses of treatment until after puberty, as they are especially prone to manifest trouble at this time.

The introduction into the spinal canal of *arsphenamized serum* by the Swift-Ellis method is held by many, notably by Fordyce, to be of value in the treatment of cerebrospinal syphilis. For this purpose, blood is withdrawn from the patient about twenty minutes after administration of arsphenamin, and on the following day 15 to 25 c.c. of the inactivated serum from this blood is administered intraspinally by lumbar puncture.

The Herxheimer Reaction.—It is probable that all effective antisyphilitic medication produces, at least momentarily, a localized hyperemia and edema in the syphilitic tissues, especially around the blood-vessels. This is called the Herxheimer reaction. It is occasionally lasting and may lead to pronounced symptoms. Thus, after the first injection of arsphenamin (rarely after mercury), a skin eruption may become greatly accentuated, or an apparently normal skin may become covered with an erythema. This eruption usually appears immediately and lasts a few hours, but it may develop later and persist one or two days. The same response of tissues infected with the treponema occurs in the internal organs. This reaction of the inner organs, which is sometimes so severe as even to threaten life, comes most frequently after the second or third dose of arsphenamin. It is most severe in syphilis of the central nervous system. As a result of this reaction an asymptomatic meningitis can, after two or three doses of arsphenamin, suddenly become typical severe meningitis.

When the Herxheimer reaction occurs in a cranial nerve it may lead to paralysis if it involves that part of the nerve which lies in a bony canal. This *neurorecidive*, as it is called, is especially frequent in the facial and auditory nerves. Such a reaction is an indication for energetic and prolonged treatment.

Cure.—To permit the assumption of complete cure, at least two full years without symptoms and without medication must elapse after completion of treatment. During this time the Wassermann reaction must be constantly negative. Furthermore, no patient should be discharged as cured until his spinal fluid has been examined and found normal. Even then it is wise to recommend examination of the blood and spinal fluid five and ten years later.

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YAWS

(*Frambesia*)

Definition.—Yaws is an infectious tropical disease which is closely related etiologically and clinically to syphilis, but is non-venereal and non-hereditary. It is characterized by early papillomas of the skin and by late destructive lesions of the skin and bones. It does not involve the nervous system.

History.—Yaws was first described in recognizable form by European authors after the discovery of America. At present it is prevalent in the West Indies, the northern coast of South America, tropical Africa, southeastern Asia, the East Indies, and the Islands of the Pacific. In the Philippines and in the West Indies the disease presents a public health problem of first rank. Yaws is relatively common and mild in childhood, and in some places, according to tradition, children are intentionally infected in order to produce immunity early in life.

Yaws and Syphilis.—Aside from its practical importance, yaws has a considerable theoretical interest because of its resemblance to syphilis. Yaws has been called "Stone Age syphilis," and the evolutionist can construct suggestive lines of descent for different strains of spirochetes. A few authors, such as Butler, see no essential difference between the two diseases, but most observers believe that syphilis and yaws, though biologically related, are distinct in etiology, pathology, and clinical manifestations. Both diseases have been repeatedly observed in the same person. On the other hand, recent epidemiological and experimental studies show that a long-continued infection with yaws does cross-protect, to a certain extent, against syphilis.

Etiology.—Yaws is an infection with *Treponema pertenue* (*Spirocheta pertenuis* or *pallidula*). This organism was discovered by Castellani in 1905 as a direct sequel to the discovery of *Treponema pallidum* by Schaudinn and was found by examining smears prepared with Giemsa's stain. The two organisms are indistinguishable in routine examinations. Minute differences have, however, been detected. *Treponema pertenue* is stated to be less rigid than *Treponema pallidum* and less regular in its twists. It stains more readily. It has been cultivated under anaërobic conditions by Noguchi.

Experimental Lesions.—A characteristic edematous lesion can be pro-

duced on the eyebrow of monkeys by inoculation with the exudate of a yaw. Rabbits can also be infected in the testicle and scrotum, as Nichols has shown. These lesions are milder than those of experimental syphilis in the rabbit and are more apt to be multiple. Nichols has been able to show that experimental yaws in the rabbit may be cured by a dose of arsphenamin which does not cure the experimental lesions of syphilis.

Morbid Anatomy.—The "yaws" are all edematous papillomas from which a large amount of serum exudes. This dries and forms the characteristic yellow crust. The organisms are found chiefly in the hypertrophied epithelium, but the first lesion develops in the papillæ of the corium. The characteristic cellular reaction is mononuclear, but if there is a secondary pyogenic infection, polynuclear cells also appear.

Symptoms.—Frequently the first symptom of yaws is the gradual development of a single papilloma, starting about three weeks after the spirochete has been acquired by direct or indirect contact with an infected individual. This primary lesion, or "*mother yaw*," very rarely occurs on the genitals, but is frequently seen around the mouth, especially in children. The regional lymph-glands enlarge and, after a longer secondary incubation period, the appearance of multiple lesions all over the body is accompanied by slight fever and rheumatic pains. In contradistinction to the chancre and roseola of syphilis, the primary and secondary yaws all have the same character. The lesion is at first a papule, which later takes on a fungoid appearance suggestive of a raspberry, from which a seropurulent fluid exudes. Later the papules are covered by a yellow crust.

In some cases auto-inoculation is responsible for the spread of the lesions and the disturbance remains confined to a small cluster of yaws at the original point of infection. The disease runs a chronic course and gradually subsides as the immunity increases. In some sites, as on the soles of the feet, yaws may persist for years in painful cracks in the tough skin.

There is no evidence of involvement of the *nervous system*, and the spinal fluid remains normal.

The *Wassermann reaction* becomes strongly positive during the early stage in 100 per cent. of cases and often remains positive in the latent period.

Swellings of the bones of the arms and legs may occur. These are demonstrable by the *x*-ray and are due to a rarefying ostitis.

The *late lesions* consist of extensive ulcers and scars and, occasionally, of a terribly destructive lesion of the nasopharynx, known as *gangosa*. Recently juxta-articular nodules have been shown to contain a spirochete which most observers accept as *Treponema pertenue*.

Diagnosis.—In an endemic region, early cases can be readily diagnosed by the distinctive appearance of the lesions. The specific diagnosis is also made easy by the presence of many spirochetes in the lesions; these organisms can be found by dark-field examination, or in smears treated with a strong polychrome stain. Sporadic and atypical cases are more difficult to recognize, as the lesions may resemble those of blastomycosis or leishmaniasis, or one of the many ulcers of the tropics. Microscopic examination may narrow the diagnosis to yaws or syphilis, but only the history of the patient or animal inoculation can provide evidence for definite differentiation, because the appearance of the organism and the Wassermann reaction are similar in both diseases. The late lesions may be confused with those of leprosy and leishmaniasis.

Prevention.—Rapid cure of infectious lesions by spirocheticides is the greatest single preventive measure. Improved hygiene and a reduction of the number of flies are secondary measures. Sellards, after a large experience in the West Indies and in the Philippines, says, "In conclusion, we have no hesitancy in selecting yaws, without reservation, as the one outstanding disease of the tropics through which the immediate confidence and enthusiasm of the people can be secured in public health work. It fulfils in very fair measure the varied psychological and scientific requirements essential to the control of an infectious disease."

Treatment.—The use of arsphenamin in the treatment of yaws is one of the greatest successes of chemotherapy, and yields such dramatic results that clinics among natives are soon overcrowded. Two intravenous injections are sufficient to cure most patients. The possibility of relapse has not, of course, been investigated as carefully as in syphilis, but, as far as is known, the disease can be permanently cured in a short time. *Mercury* has practically no effect in the early stages; the papules can be resolved by local applications of *silver nitrate.*

On account of the expense of arsphenamin many other drugs have been tried. *Sodium and potassium bismuth tartrate* is much cheaper, and when administered intramuscularly is fairly effective. *Antimony* (by mouth) and *sulpharsphenamin* (subcutaneously) are also helpful. With the reduction in the cost of arsphenamin, and the increasing skill in intravenous injections, the tendency is to rely on the most specific treatment.

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DISEASES DUE TO PARASITIC INFUSORIA

BALANTIDIASIS

Balantidiasis is associated with *Balantidium coli* and is the only important infusorian infection of the human being. Infections with other ciliates are extremely rare, many of those reported being based on misinterpretation of the presence of non-parasitic or free-living organisms in stools or urine. Since the disease was first recognized in man by Malmstein in 1857, many cases have been observed in practically all parts of the

world and in both cold and warm climates. A considerable percentage occur in the United States, as well as in countries of Central and South America. Nothwithstanding its wide distribution, balantidium dysentery is relatively rare, as is shown by data obtained from wide-spread examination of stools during recent years.

The organism which infects man is *Balantidium coli*, a parasite for which the domestic pig serves as the normal host. Recent work by McDonald tends to show that the pig harbors two species of Balantidium, *B. coli* and *B. suis*, but it is apparently only the former which establishes itself in the human being. Spontaneous infection with Balantidium has also been observed in apes, and monkeys and young pigs have been experimentally infected with material from man. The pig is, however, undoubtedly the reservoir from which human infection is derived.

Balantidium coli is a relatively large organism which measures from 30 to 200 micra in length and 20 to 70 micra in breadth. It is ovoid in form and at the more pointed anterior end there is a funnel-shaped mouth through which food particles are taken into the cytoplasm. The surface is covered with a dense cuticle marked with longitudinal lines in which cilia are set at regular intervals. The macronucleus is large and kidney shaped; the micronucleus, small and usually situated within the indentation of the larger. The cytoplasm contains two contractile vacuoles and particles of food often of the nature of starch granules. Red blood-corpuscles and other cells are also taken as food under certain circumstances. The residuum after digestion is extruded through a break in the cuticle at the posterior end.

Reproduction is accomplished by transverse binary fission of the active ciliated organism. Encystment of the organism either singly or in pairs occurs. It has been shown by experiment that the free motile forms soon perish outside the body and are destroyed by the digestive juices on ingestion. The cysts, on the other hand, are quite resistant, but do not withstand drying. These must be considered infective forms.

Considering the frequency and degree of contamination of the hands and food with the excrement of pigs, the rarity of the infection in man is notable. Mere ingestion of the encysted organism is of itself apparently insufficient to cause infection, and Brumpt suggests that changes in diet or in the reaction of the intestinal contents may make infection possible.

Morbid Anatomy.—The pathogenicity of this parasite for the host to which it is poorly adapted (the human being) is greater than for its normal host, the pig, in which it habitually lives in the contents of the cecum and large bowel. In man it quite frequently invades the wall of the large intestine.

At postmortem examinations the large intestine is seen to have undergone ulceration of varying degrees; this is usually rather superficial and without marked infiltration. The Balantidia penetrate the tissues for a considerable distance from the ulcers and are present in the lymphatics, and occasionally in the blood-vessels. There is no notable reaction of the tissue around living parasites, possibly on account of their active motion, but when they degenerate and die, lymphoid and plasma cells accumulate locally. The lesions in the mucosa are often small, fistulous in character, and suggest the passage of numbers of the organisms along definite paths. The dissemination of Balantidium through the blood-stream to various organs has been reported.

Symptoms.—Frequently individuals harboring the parasite show no symptoms. The invasion of the tissues by the parasite produces symptoms of colitis characterized by diarrhea, and the presence of more or less blood and mucus in the stools. Balantidiasis is a chronic infection and has been reported to persist for as long as twenty years. In order to avoid misinterpretation of the significance of the presence of the *Balantidium coli* it should be borne in mind that carriers may be afflicted with other infections, or that they may harbor other parasites which produce disturbances. The possibility of the spread of the organism to lymph-nodes, and, via the blood-vessels, to the liver, lungs, and other organs should not be forgotten.

Diagnosis is based on the presence of *Balantidium coli* either in its free motile stage or in its encysted form in the stools. On account of their large size and striking appearance the motile forms are very readily recognized.

Treatment.—No *drug* specific for this disease has been discovered. Lavage of the colon by enemas containing quinin, thymol, turpentine, salicylates, or tannic acid is without benefit; and other substances, such as calomel, phenyl, salicylate, arsphenamin, ipecac, and emetin have also been tried, without marked success.

Recently Green and Scully have advocated careful adjustment of the diet as a beneficial therapeutic measure. The patient is at first given milk only (in amounts up to $2\frac{1}{2}$ quarts a day) in small portions, at frequent intervals. After several days this is supplemented by one or two eggs. If dysenteric symptoms are pronounced, bismuth subnitrate may be administered; if constipation develops, cooked fruits should be given. Under this régime the symptoms are said to subside and the parasites to disappear from the stools. There is no tendency to relapse.

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DISEASES CAUSED BY TREMATODES OR FLUKES—DISTOMIASIS

Platyhelminthes (flat worms) are divided for purposes of classification into several classes, of which only the *Trematoda* (the sucking worms or flukes) and the *Cestoda* (tapeworms) are of pathological importance. Flukes are non-segmented and are commonly leaf-shaped or tongue-shaped, although certain species have other peculiarities of contour. Suckers are present in all species. The Trematodes which occur in man possess in addition to an oral sucker, or mouth, a ventral sucker or acetabulum. The largest human fluke, *Fasciolopsis buski*, may grow to 75 mm. in length. *Heterophyes heterophyes* measures no more than 2 mm. in length. In some species the cuticle is smooth, in others, provided with spines. There is

no body cavity, the internal organs being embedded in a sort of connective tissue. Most flukes are hermaphroditic, but in certain instances, as, for example, the blood flukes, the sexes are distinct. Auto-copulation and fecundation as well as cross-copulation occur. The eggs of all flukes, except the Schistosomidæ or blood flukes, are operculated, and on many there is a small knob or rudimentary spine near the non-operculated extremity.

Life-cycle of Flukes.—All flukes which are parasitic in the human being multiply both by the production of fertilized eggs and by a sort of internal budding which produces one or more asexual generations. The latter form of reproduction, so far as is known, always takes place in certain species of mollusk which serve as intermediate hosts. The eggs of many species of flukes are ripe when discharged, so that if placed in ordinary fresh water the ciliated embryo or miracidium emerges from the shell. The complete life-cycle has been determined for comparatively few species, but there is considerable evidence to show a great similarity in the development of many others. The miracidium on escaping from the shell is attracted to certain species of snails which serve as intermediate hosts. After penetrating these, the fluke assumes a gutless form known as the *sporocyst*. Within the sporocyst groups of cells (germ balls) appear, which form a generation of organisms termed *rediæ* within which a brood of cercariæ develop. In some instances two generations of rediæ are produced. The rediæ are distinguished from the sporocyst by the fact that they possess a primitive alimentary tract consisting of mouth and simple tubular intestine. The cercariæ are still more differentiated, having mouth, pharynx, and bifurcated intestine, as well as an acetabulum. The parasite at this stage is equipped with an active caudal appendage by which it propels itself through the water. The cercariæ may finally become encysted and, after ingestion by the proper host, proceed to develop into mature flukes. *Encysted cercariæ* are variously distributed in various species, *i. e.*, in water, on plants, in certain animals serving as secondary intermediate hosts, or in the first intermediate host where they become encysted within the sporocyst instead of swarming out as in other cases. Certain cercariæ, those of the blood flukes, do not encyst, but actively penetrate the skin and mucous membranes of their definitive host.

DISEASES DUE TO INTESTINAL FLUKES

(*Intestinal Distomiasis*)

Fasciolopsis buski (Lankester, 1857) is by far the most important of the intestinal flukes which are found in man. It is a large form (30–75 mm. in length, 10–15 mm. in width) and quite thick. The large ventral sucker has a pear-shaped opening. The branched ovary and shell gland are central and just anterior to the branched testes; the coiled uterus is anterior to the testes. This species is characterized by a long cirrus pouch. The eggs are large, averaging 125 micra in length and 75 micra in width. Goddard, after a painstaking study of *Fasciolopsis*, has concluded that the flukes described as *F. rathouisi*, *F. goddardi*, and possibly *F. fulleborni* are all of the species *F. buski*. The variation in the shape and appearance of specimens in various states of contraction and degrees of maceration and also the tendency of the cuticle and its spines to separate probably account for erroneous distinctions. Its *habitat* is the small intestine and to some extent the stomach of the human being and the pig; in certain regions it is very prevalent in both.

The *development*, which is somewhat similar to that of flukes in general, has recently been followed in detail by Barlow. According to Nakagawa, the eggs must remain in water two or three weeks before hatching. The miracidia on hatching penetrate either of two small species of snails, one of the genus Planorbis, the other a Segmentina, and produce generations of rediæ which, in turn, give rise to cercariæ. The latter leave the snail and become encysted on aquatic plants, especially on the water caltrop and the so-called water chestnut. These water nuts, being customarily eaten raw,

serve as vehicles for the introduction of the encysted cercariæ into the intestine, where they grow into mature flukes.

Incidence.—The use of freshly passed human excrement for fertilizing the above-named water crops doubtless favors infection with this parasite wherever proper intermediate hosts abound. *Fascialopsis buski* is apparently widely distributed, having been recognized in India, Assam, Siam, Natal, Borneo, Straits Settlements, Sumatra, Cochin-China, Tonkin, and in parts of China. It is especially frequent in Shaohing, where its ova have been found in the feces of 95 per cent. of hospital patients. Goddard has estimated that in certain regions 5.5 per cent. of the entire population harbor the parasite and that 2 per cent. have symptoms.

Symptoms.—Individuals may harbor small numbers of this parasite without developing symptoms, but the presence of a considerable number of the flukes sooner or later gives rise to a well-defined syndrome. Three stages of the disease are recognized:

1. The period of latency in which there are no pronounced symptoms. Probably more or less asthenia precedes the recognition of the disease.

2. The period of diarrhea in which medical aid is first sought. There may be more or less diarrhea for months and varying degrees of abdominal pain. The stools are light yellow and do not contain blood. According to Barlow, anemia does not commonly occur, but is simulated by the transparency of the edematous tissues. Wherever the disease is endemic, diarrhea combined with edema is almost pathognomonic, although the feces must be examined for the specific ova to establish definitely the diagnosis.

3. The period of edema. The edema becomes more distressing, and it usually affects various parts of the body in the following order: the abdominal cavity, the genitalia, and the lower extremities, beginning in the feet and ankles, but including the whole limb, and finally involving the face and the lungs. Cardiac insufficiency may supervene in the late stages of the disease. The skin becomes harsh and dry and has a yellow tinge; the tongue is coated. The urine is normal except for undue concentration. The temperature tends to be subnormal. Death, when it occurs, is apparently due to exhaustion.

Treatment consists primarily of the administration of drugs to expel the flukes. *Paracentesis abdominis* may, however, be necessary to relieve dyspnea. Chloroform, thymol (4 to 8 gm. in 1 gm. capsules at intervals of one hour), and β-napthol have all been used successfully. Goddard prefers the latter drug and believes that it is better to administer small doses of whatever drug is employed. The diet should be restricted and saline purgatives given both before and after administration of the remedy. During treatment the patient should remain in bed. If thymol is used, such solvents as oils, alcohol, and chloroform should be wholly avoided to prevent serious intoxication. Dead flukes begin to be passed within twelve hours of the administration of the anthelmintic and the patient usually shows prompt improvement. Barlow finds carbon tetrachlorid to be the most efficacious remedy, but points out that its use is attended with danger.

Other Intestinal Flukes.—In addition to *Fasciolopsis buski* several other intestinal flukes are found in man. *Watsonius watsoni*, 8 mm. in length, is reported from northern Nigeria, and is said to be common around Lake Chad. *Gastrodiscus hominis*, a fluke with a cup-like posterior extremity, has

been observed a few times in man, and it is probably quite prevalent in India and Assam. This species has been associated with dysenteric symptoms. *Heterophyes heterophyes*, a very small fluke (2 x 0.5 mm.) is apparently quite common in Egypt. It was found by Looss in 2 out of 9 autopsies. Another minute intestinal fluke, *Metagonimus yokogawai*, is prevalent in Formosa and is found in Japan. It has been seen also in China by Leiper. *Echinostoma ilocanum* and *E. malayanum* have been found in the human intestine in the Philippines and in the Malay States, respectively.

TREMATODE INVASION OF THE BILE-DUCTS

(*Hepatic Distomiasis*)

Clonorchis sinensis, the most important liver fluke in man, occurs in southern and eastern Asia, especially in parts of China, and in certain districts of Japan. Leger found that in Tonkin 50 per cent. of apparently healthy persons harbor flukes of this type. It has been asserted that symptoms are produced only when the parasites are present in great numbers. There is, however, considerable evidence that this species has definite pathogenic properties. The changes in the bile-ducts which are associated with these flukes are evidence of their effect on the body, and it is apparently a mistake to consider them harmless. More than 4000 parasites have been found in the liver of a single individual; they occur also in the pancreas, and rarely in the duodenum. The symptoms and pathology attending the invasion of the bile-ducts by various species of flukes are so similar that they need not be considered separately for each species.

Life History.—Kobayashi, in 1911, found cercaria encysted in a number of species of fresh-water fishes, which when ingested by cats grew to adult Clonorchis. The adult worms occur in fish-eating animals, *i. e.*, in man, the dog, and the cat. According to Muto (1918) the miracidia, on hatching from the eggs, are attracted to a snail, *Bythnia striatula*, in which development is completed in about three weeks, when the cercariæ are liberated. These penetrate certain species of fish and become encysted in the muscles. At this stage, the worm survives many days of chilling and withstands heating for fifteen minutes at from 60 to 70° C. Clonorchis sinensis is long lived and is reported to have persisted for twenty years in an individual who had come to live in a country where the worm occurs only in immigrants.

Morbid Anatomy.—Clonorchis sinensis, when present in large numbers in the liver, may produce profound cachexia. Attention is called by Brumpt to various ways in which liver flukes act deleteriously upon their host, for example, by robbing the host, by their mechanical action, by their irritative properties, and by toxic action resulting from their presence, as well as from associated bacteria. They feed upon the bile and probably to a certain extent on the blood and tissue juices. When present in large numbers they may obstruct the biliary ducts so that jaundice results, or because of pressure on certain veins may produce ascites or enlargement of the spleen. The pancreatic ducts may also be obstructed. Pronounced changes caused by constant or repeated local injury in the region of the bile-ducts produce a characteristic pathological picture.

The liver is probably somewhat enlarged early in the disease, but later is often contracted. Its surface is studded with pale vesicles, and on section numerous thick-walled cavities representing dilatations of the bile-ducts

are apparent. These cavities vary somewhat in size according to the species of fluke and contain numbers of adult worms and a fluid to which the presence of innumerable eggs may impart a brown color. There is not only sclerosis about the distended ducts, but also extensive proliferation of the biliary epithelium which produces an adenoma-like tissue. The modified epithelium ordinarily shows no invasive properties, although Askanazy has reported instances of malignant new growth resulting from the presence of *Opisthorchis felineus*. The sclerosis which is always present appears to be progressive, and through interference with circulation or obliteration of ducts the corresponding portions of the liver parenchyma are secondarily destroyed. Under such circumstances vascular areas resembling angioma may appear. Associated with these destructive processes there is compensatory hypertrophy of unaffected portions of the liver.

Even more important than the destruction of liver tissue is the diffusion through the circulation of toxic material from the flukes, which may result in a severe anemia comparable to the so-called "aqueous cachexia" seen in distomiasis in sheep. Bacteria are frequently transported from the intestine into the bile-ducts during the migration of the young flukes.

Symptoms.—While in certain countries many apparently healthy individuals may discharge daily considerable numbers of the eggs of a liver-fluke, those harboring large numbers of the parasite are likely to have symptoms of some sort. The liver is sometimes enlarged and usually sensitive to pressure. Pains in the right hypochondrial region or in the epigastrium are frequent. Jaundice, epistaxis, or bloody diarrhea may appear. In the more severe cases there may be ascites, swelling of the lower extremities, and severe anemia. Death may result from the general cachectic condition which ensues.

Prophylaxis.—The prevalence of *Clonorchis sinensis* in the human being is dependent upon local customs with regard to food. In countries where uncooked fish is not eaten this parasite would not be expected to become prevalent in the human being, even though the proper intermediate hosts abounded. Thus it has been pointed out that whereas opisthorchis may occur frequently in cats in two different countries, it will be found frequently in human beings in the one in which uncooked fish forms an important part of the diet, while in the other, where this custom does not prevail, it is confined to animals.

Treatment.—This fluke is rather resistant to treatment, but encouraging results have been obtained with tartar emetic. Shattuck has met with better success when employing this drug in alternation with arsphenamin than with either one alone.

Fasciola hepatica (Linnaeus, 1758), a parasite of great economic importance by reason of its destruction of sheep, occurs only rarely in man. (Only 28 cases had been reported up to a recent date.) This fluke produces a marked adenomatous proliferation of the bile-ducts of sheep, but in man the disease has, in most instances, been mild. Liver disease is indicated by hepatic enlargement, local pain, and icterus. As the result of the custom in North Lebanon of eating raw liver the adult worms are reported by A. Khouri as attaching themselves to the pharyngeal mucosa and adjoining parts of the human throat and causing a definite symptom complex known as "*Halzoun.*" It is considered probable that the flukes which have been reported to occur in the lens of the eye in cases of cataract (*Distomum*

oculi humani, Ammon, 1833) and in other parts of the body distant from the alimentary tract, are strayed immature forms of *Fasciola hepatica*.

The life history of this species, as worked out by Thomas and Leuckart, has served as a basis for investigations of the development of other flukes attacking the human being.

Dicrocelium dendriticum, the lancet-shaped fluke, occurs in the bile-ducts of herbivorous and omnivorous animals, but less commonly than *Fasciola hepatica*. It has been reported only seven times in the human being.

Opisthorchis felineus is a fluke most frequently found in the gall-bladder and bile-ducts of the cat, but also in the dog, fox, and glutton, as well as in man. In the region of Tomsk this is said to be the parasite of man most frequently seen at postmortem examination. In a series of cases reported by Winogradoff there was enlargement of the liver in the acute stage of the disease, dilatation of the bile-ducts with inflammation and thickening of their walls, icterus, atrophy of the liver, and, late in the disease, ascites. In cases reported by Askanazy lesions regarded as carcinomatous were found in association with the flukes. Cases have been reported from various European countries, frequently from East Prussia and from Siberia and Japan.

Paropisthorchis caninus, a parasite of pariah dogs, appears to be slightly different from *Amphimerus noverca*, which was found by McConnell in the human being. The distinctive feature of the former parasite is the separation of the vitellaria into preovarial and postovarial portions. Several other species of fluke have been found in the bile-ducts of the human being, but the pathological effects of liver flukes in general are quite similar.

TREMATODE INVASION OF THE LUNG

(*Pulmonary Distomiasis*)

Paragonimus westermanni produces a well-recognized disease in Japan, Korea, Formosa, and parts of China. Cases are also reported from Sumatra and the Philippine Islands. Pulmonary involvement is commonly associated with hemoptysis. The worm is frequently widely distributed in the body, however, and produces lesions in the intestines, pancreas, liver, spleen, kidneys, bladder, epididymis, prostate, and in the choroid plexus of the brain. Dogs, cats, and other carnivors as well as hogs frequently harbor this parasite.

Paragonimus is a thick fluke about the size and shape of a coffee bean. Its eggs, which are of deep brown color and measure 85 to 100 micra in length and 50 to 67 micra in width, are discharged in the sputum.

Life History.—The eggs are discharged undeveloped, but if kept in water for several weeks develop into a ciliated embryo which finally escapes from its shell and swims free. Several Japanese investigators have shown that snails of the species *Melania libertina* are attacked by these miracidia. Sporocysts found in this snail were regarded as later stages of development. The cercariæ are found encysted in many species of fresh water crabs and crawfish which act as secondary intermediate hosts. Although there appears to be little doubt as to the recognition of the first and second intermediate host of the lung-fluke, it has not been possible to follow its complete development in them since they also harbor many other larval flukes. The subsequent development within the definitive host is readily followed by feeding crabs containing the encysted cercariæ to cats. On penetrating the intestinal mucosa, they migrate through the tissues to the lungs and occasionally to other organs, passing *en route* through the peritoneal cavity, the diaphragm, and pleural cavity.

Iturbe has reported that in Venezuela the snail, *Ampullaria luteosoma*, serves as first intermediate host for *Paragonimus*, and the crab, *Pseudothelpusa iturbei*, as second.

Morbid Anatomy.—The simplest lesions consist of mild inflammatory changes around collections of eggs. The worms are situated within cysts of a size sufficient to admit the tip of the finger. In the human being, such cysts may frequently contain only one worm, but in the dog, each commonly contains two. The lesions are infiltrated with eosinophils. Certain lesions undergo caseation and resemble tubercles, and abscesses and ulcerations occur frequently. Associated with these lesions there may be extensive cirrhotic changes, bronchiectasis, and emphysema.

Symptoms.—Musgrave, who found 17 cases of the disease in the Philippines during one year, recognizes the following forms of the disease: (1) The generalized type, which is associated with fever, enlargement of the lymph-nodes, muscular pains, and ulceration of the skin; (2) the thoracic type, which is characterized by cough, blood-stained or purulent sputum, in which the eggs, or more rarely an adult distome, may be present, and associated with thoracic pain, in some cases with signs indicating bronchopneumonia or pleuritic effusion; (3) the abdominal form in which there is more or less pain and tenderness, but less distinctive symptoms except when certain organs are acutely involved, as in appendicitis, epididymitis, diarrhea associated with intestinal ulceration, and cirrhosis of the liver; (4) the cerebral type which appears to be frequently associated with epilepsy and sometimes with paralysis and neuritis.

Diagnosis.—The diagnosis is established by demonstration of the eggs in the sputum, feces, or fluids obtained by puncture. The prevalence of the disease must also be taken into account in making the diagnosis.

Treatment.—There is no specific treatment, but administration of iodid of potash is recommended by Musgrave. Brumpt suggests emetin on account of its efficacy in the treatment of other diseases due to trematodes. Human beings undoubtedly acquire paragonimiasis either by eating raw or partially cooked crab meat containing the encysted cercariæ or by drinking water into which the cysts have been liberated from disintegrating crabs.

THE BLOOD FLUKES (HEMIC DISTOMIASIS, BILHARZIASIS)

The flukes infesting the blood-vessels are of the family *Schistosomidæ* in which the sexes are separate. They commonly occur in pairs. The male is of whitish color, flattened, with the lateral borders rolled ventrally to form a gynecophoric canal for the accommodation of the female. The female is longer than the male and, being slender and rounded, appears somewhat thread-like. The presence of considerable amounts of partially digested blood in the intestinal tract gives the female a dark color, especially in the posterior portion of the body.

Three species occur in the human being—*Schistosoma hæmatobium, S. mansoni, and S. japonicum.* They show no marked difference with respect to size; *S. japonicum* is the smallest—males 9 to 12 mm. and females 12 to 15 mm. in length—while in *S. hæmatobium* the males measure from 10 to 15 mm. and the females 15 to 20 mm. in length. These species are readily distinguished by the type of egg which they produce; thus that of *S. hæmatobium* has a sharp terminal spine, that of *S. mansoni,* a lateral spine, while that of *S. japonicum* is broader and has no spine.

Schistosoma hæmatobium is widely distributed throughout various parts of Africa and to some extent in Asia Minor, certain localities being notorious

for its prevalence. There is a claim that it is present in Egyptian remains from the twelfth dynasty, possibly 2000 years B. C. The parasite is found in the adult state in the veins of the submucosa of the bladder, less frequently in the hemorrhoidal veins, and more rarely in the region of the appendix. Immature forms, in various stages of development, are also found throughout the portal system, whence they evidently migrate against the blood-stream through the inferior mesenteric vein, through the inferior and middle hemorrhoidal veins and plexuses and, by passing through communicating veins, reach the bladder wall. Although not fully developed, the worms occur in pairs in the portal system. Eggs deposited here are carried in the blood-stream to the liver, where they are found in considerable numbers after death. On reaching the bladder wall, the migration of the worm is governed by the caliber of the veins. Since the male worms measure 1 mm. and the female 0.28 mm. in thickness, they are unable to pass through the small veins (0.04 mm. in diameter) which supply the mucosa of the bladder. They thus occur in pairs in the veins of the submucosa. That an endophlebitis is set up, enclosing the worms in copula, may to some extent account for the fact that the eggs are not swept into the circulation when deposited. Instead they tend to work their way through the mucosa of the bladder so that they are discharged in considerable numbers with the urine. Since the eggs are purely passive foreign bodies, it is difficult to explain their escape from the mucosa. Probably their passage through the tissue is aided by the alternate distention and contraction of the bladder. Minute fistulous passages through the mucosa also favor their escape.

Development.—Until recently, nothing was known of the development of the worm subsequent to hatching of the miracidium in water. The Bilharzia mission to Egypt, headed by Leiper, demonstrated that subsequent stages of development occur in fresh-water snails, *Bullinus contortus* and *Bullinus dybowski* found in Egypt. Cawston found *Physopsis africana* naturally infected in Natal. In countries around the Mediterranean other species of snails may harbor the larval forms of *Schistosoma hæmatobium*. The generation of free-swimming cercariæ, which escape from these mollusks, may enter the body of experimental animals and presumably of man, by way of either the skin or the alimentary tract. This supports the firmly founded belief, in regions where the parasite is common, that schistosomiasis may be contracted from certain bathing places. Allen in 1888 reported that boys bathing in certain pools became infected, while girls not exposed in this way show infection more rarely.

Morbid Anatomy.—The bladder in the early stages shows either diffuse reddening or local hyperemia and swelling. The impregnation of areas of the mucosa with eggs may give it a sanded appearance. Ulceration may occur. Swelling and hypertrophy of the mucosa produce papillomata which may in some cases very closely simulate adenomata. In some instances, the ureter becomes involved and obstruction follows thickening of its wall. The process may extend to the prostate, the urethra, or outward above the pubis and through the abdominal wall, the tissue being in each case infiltrated with ova, the so-called bilharzial tissue. The disease is frequently associated with calculus and may be further complicated by bacterial invasion. The thickening of the bladder wall and the papillomatous condition of the mucosa are conducive to stagnation and decomposition of the urine. If worms lodge in the hemorrhoidal veins, a similar hyperplastic condition may be found in the rectum. More rarely the colon or the appendix vermiformis alone may be involved.

Symptoms.—Many individuals harbor *S. hæmatobium* for many years

without notable inconvenience, although they pass small clots of blood regularly in the urine. Some degree of hematuria is common, but not invariable. The blood may contain from 10 to 20 per cent. of eosinophilic cells. With calculus, ureteral obstruction, urethral abscess, and sepsis, the symptoms become severe, and the disease may be associated with most intense suffering. Dysenteric symptoms with severe tenesmus may accompany rectal involvement.

Diagnosis.—The diagnosis is based on the presence of terminal spined eggs in the urine or feces. According to Cawston, the disease in Natal is usually mild and many patients have practically no symptoms.

Prophylaxis.—Prophylactic measures are now clearly indicated and suspicious water should be treated both for drinking and bathing purposes. Measures taken for the eradication of the snails prove effective because the free-swimming cercariæ are short lived, and die within forty-eight hours if they fail to reach their definitive host. Leiper has recommended the periodic emptying and drying out of the irrigation canals in the cultivated lands of lower Egypt in order to destroy the snails. Ponds and other bodies of water may be treated with copper sulphate or sulphate of ammonia; the former in a dilution of 1 to 5,000,000 is sufficient to kill Bullinus.

Treatment.—Until recently no remedy had been found which would destroy the *Schistosoma hæmatobium*. After persisting for a variable length of time it often disappears spontaneously. The intravenous injection of *tartar emetic*, first employed for the treatment of schistosomiasis by MacDonagh and Christopherson, has, however, proved of considerable value. A 1 per cent. sterilized solution in physiological salt solution is administered in increasing doses (5, 7.5, up to 10 c.c.), the injection being made every other day until a total of 75 c.c. has been given. It is necessary to proceed cautiously with this medication, for some patients show a pronounced intolerance for the drug, which is evidenced by salivation, dizziness, and vomiting. This method of treatment is not devoid of danger, for the accumulation of tartar emetic in the internal organs may produce serious injury, as, for example, lesions of the liver. Under favorable conditions the worms evidently die, for the eggs disappear from the urine.

Symptomatic treatment varies with the nature of the complications; in the majority of cases it is unnecessary. The presence of calculi or polypoid masses, involvement of the ureter, etc., may require surgical measures.

Schistosoma mansoni, which occurs in the various parts of Africa, is also endemic in the West Indies, certain regions of South America, and possibly in other parts of the world. These worms are more closely restricted to the mesenteric veins: *S. hæmatobium* is most commonly found in the pelvic veins. The intermediate host of *S. mansoni* is, in Egypt, *Planorbis boissyi*, and in South America, *Planorbis guadelupensis* (Iturbe and Gonzalez). Animals may be infected by immersion of the skin in water containing the free-swimming cercariæ or possibly by the ingestion of the parasites during this active stage.

Morbid Anatomy.—Many cases of intestinal schistosomiasis are mild and there are only minor pathological changes. Infiltration of the intestinal mucosa with eggs tends, however, to produce ulceration and polypoid masses. The latter are especially prone to develop in the rectum and descending colon, where they assume cauliflower-like form. The transportation of eggs by the circulation to the liver results in more or less

chronic inflammation and often in an increase in the hepatic connective tissue about the portal canals.

Symptoms characteristic of chronic dysentery are not uncommon. Emaciation and colic frequently accompany the development of extensive lesions associated with deposition of eggs in the intestinal mucosa. It is claimed, evidently on the ground that reinfection may occur, that recovery is favored by removal from the region where the disease is endemic.

Treatment.—The treatment is essentially similar to that employed for *S. hæmatobium.*

Schistosoma japonicum occurs in Japan, parts of China, and the Philippines. It causes a very serious condition known in Japan as *"Katayama" disease,* characterized by diarrhea and dysenteric symptoms, painful enlargement of the liver and spleen with or without fever, dropsy, anemia, and occasionally pulmonary or cerebral symptoms. The chief injury is produced by the deposition of the ova in the walls of the intestine, the liver, the spleen, the lungs, and occasionally in the brain. They are found in large numbers in the mucosa and submucosa of the greatly thickened intestine, but may also be distributed beneath the serous coat of the small intestine, where they give rise to polypoid masses. The invasion of the skin of workers in the rice fields by the cercarial stage of the worm produces a skin disease known locally as *"Kabure."*

Development.—According to Narabayashi and other investigators the miracidia, after hatching from the egg, penetrate a snail (*Blanfordia nosophora*) found in rice fields, and there undergo further development. The cercariæ, after leaving the snail in which asexual multiplication takes place, may penetrate mammalian skin and then migrate to the portal vein. This species occurs in cattle, dogs, and cats as well as in man. The life history of this parasite, as worked out by Miyairi and Tuzuki, was confirmed in 1914 by the findings of the Wandsworth Expedition of the London School of Tropical Medicine (see also Cort).

The snail which serves as the intermediate host of *S. japonicum* lives in the mud and vegetation of the irrigation ditches of the rice fields and is destroyed with difficulty. It withstands drying for many weeks. The application of quick-lime is about the only effective measure which does not interfere seriously with agriculture.

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DISEASES CAUSED BY CESTODES—TENIASIS

The class Cestoda (tapeworms) are endoparasitic flat worms without an alimentary canal, generally hermaphroditic, and segmented in the adult state. They are typically ribbon-like, being composed of a head portion and a chain of segments, each of which contains sexual organs, which eventually become so developed that they replace most other structures. The head is adapted for adhesion or fixation to the host. The body is covered with a cuticle, the cells of which are embedded in the parenchyma or supporting tissue. The excretory system is symmetrical and open at the posterior end. Nutriment is absorbed through the surface of the body. Adult tapeworms are parasitic in vertebrates, while the larval forms occur in both vertebrates and invertebrates.

Whether the tapeworm represents an individual, or a colony of individuals all derived from the parent head portion (scolex), is a question which has been the subject of much discussion. However the entire tapeworm (strobila) is regarded, the fact remains that the scolex, being composed largely of actively growing germinative tissues, continually gives rise to new segments (proglottides), which commonly form a long chain. The young undifferentiated proglottides are, therefore, near the scolex where segmentation is taking place; those further away, contain differentiated sexual organs; those near the end of the chain are ripe and filled with ova. The proglottides may, in some species, form a chain composed of several thousand segments, while in others, only a few remain attached to the scolex. In most species, however, ripe segments (either singly or in groups) eventually separate from the parent chain and are found in the stools. Since the head is continually producing new segments, it is obvious that any course of treatment that fails to detach it must be ineffective.

The terminal portion of the *scolex* is provided with muscular suckers (acetabula), or muscular grooves (bothria), and in some species, with hooklets, or other structures, which permit adhesion or fixation to the host. This portion of the scolex is termed the head, and the following nonsegmented portion, the neck. The head is said to be armed or unarmed according to whether or not it is provided with hooklets. The *segments* are usually flattened and quadrilateral in outline, but the lateral borders frequently bulge.

The *adult worms* occur in the alimentary tract of vertebrates, and in mammals, are almost wholly restricted to the small intestine. The eggs of species possessing a uterine pore are discharged into the intestinal contents, but those of other species are liberated when the segments disintegrate either in the feces or outside the body. For most tapeworms a secondary host is necessary—either another vertebrate or, in some instances, an invertebrate. Fecundation may be accomplished either through copulation between the segments of different worms or between different segments of the same worm; auto-fecundation may also take place.

Two different types of eggs are produced. The *Diphyllobothriidæ* produce ovoid, operculated eggs containing fertilized ovum and yolk cells. The eggs of other tapeworms have a more complicated structure and development: they consist at first, of fertilized ovum and yolk cells enclosed within a delicate shell; later, an embryo develops and a rather thick secondary membrane is formed upon its surface; further development only takes

place after the embryo is ingested by its proper intermediate host. In the alimentary tract of this animal the embryo escapes from the membrane and penetrates the tissues, where it develops into the larval stage.

Larval tapeworms are classified as *plerocercoid* when elongated and worm-like, and *cysticercoid* when bladder-like. Those of the latter type are further classified as *Cysticercus*, when only a single scolex develops in the bladder-like larvæ; *Cœnurus* when several scolices are developed; and *Echinococcus* when the larva produces daughter cysts, granddaughter cysts, or brood cysts with numerous scolices. In order that such larval forms may develop, their ingestion by the primary host is necessary. This is ordinarily accomplished through the eating of uncooked flesh.

Certain tapeworms are apparently not markedly injurious to their host. Others give rise to toxic products which may produce profound anemia. The larval forms developing in various organs may also produce serious complications.

The **families of tapeworms** infesting man are principally the *Diphyllobothriidæ*, the *Hymenolepididæ*, and the *Tæniidæ*.

The DIPHYLLOBOTHRIIDÆ are represented by species of two different genera that are parasitic in the adult state in man. In rare cases the body of the human being is invaded by plerocercoid larvæ, the adult form of one species of which has recently been discovered.

Diphyllobothrium latum (*Dibothriocephalus latus*), the so-called *"broad tapeworm"* or *"fish tapeworm,"* is widely distributed in Europe, especially around the Baltic, in Poland, Roumania and Switzerland, and occasionally in other regions; it is said to be especially common in Japan and Turkestan, is reported from parts of Africa, and has established itself in a localized area in the United States (Minnesota). This worm is long lived, and is known to have lived in the human being for as long as sixteen years. Consequently, it is frequently seen in regions far removed from those in which it was acquired by the human host.

There are usually no serious symptoms associated with the presence of this worm, at least for long periods. Not infrequently, however, it causes a very severe anemia which closely resembles pernicious anemia, except that improvement and recovery usually follow the expulsion of the worm.

Diphyllobothrium latum measures from 2 to 9 meters and is of whitish-gray color with a yellowish tinge. The head is almond-shaped and flattened laterally with deep grooves or bothria in its dorsal and ventral borders; the neck is very slender. The proglottides may number 3000 or 4000 and, with exception of the older segments, are broader than they are long.

The eggs are large and ovoid, with thick brownish shells having inconspicuous lids. The embryo is only slightly developed and surrounded by yolk cells. In from seven to ten days after the eggs are deposited in water the shells are burst by the ciliated organism which has developed within. This enters a fresh-water crustacean, *Cyclops strenuus*, to undergo further development. The plerocercoid, however, is found in various species of fresh-water fish, and it is by ingestion of the raw or improperly cooked infested fish that man acquires the parasite. The adult worm also occurs in the dog, the fox, and the cat.

Diphyllobothrium parvus is a comparatively small worm, its largest segments measuring only 5 x 3 mm. The eggs average 59.2 x 40.7 micra. This species has been reported in a Syrian in Tasmania.

Diphyllobothrium cordatus is commonly found in seals and dogs in Greenland. It is rare in man.

The genus Diplogonoporus is characterized by a short scolex with powerful suctorial grooves and no neck. The segments, which are short and broad, each contain two sets of genital organs which are essentially similar to the single structure of the common "broad" tapeworm. *Diplogonoporus grandis* occurs in the adult state in whales and seals, and has been found in the human being in Japan.

Bothriocephalid larvæ have been found several times in man. Since the adult forms were unknown, the generic name *Sparganum* was applied to them. *S. mansoni* was discovered by Patrick Manson in an autopsy on a Chinese. This parasite, although comparatively rare in the human being, appears to be widely distributed throughout the world. It has been reported in regions of Africa, Australia, the Caribbean Sea, English Guiana, and the southern United States, as well as in China and Japan. The plerocercoids are somewhat ribbon-shaped, may attain a length of 30 cm. and a width of from 3 to 12 mm. They have been found beneath the peritoneum, in the abdominal cavity, in swellings of the skin, and in the urine. They are most frequently seen about the eye and in the genito-urinary tract. Through the investigations of Japanese parasitologists, the complete life history of this worm is now known. The adult *Diphyllobothrium mansoni* occurs in dogs, while the larval plerocercoids are distributed in various animals, *i. e.*, man, hogs, monkeys, cats, rats, chickens, ducks, snakes, and frogs.

Sparganum proliferum produces an acne-like lesion of the skin and may be present in great numbers throughout the various organs and tissues of the body. It is characterized by its irregular shape, numerous heads being produced which become detached and wander through the tissues. It has been reported from Japan and Florida. The adult form is unknown.

Dipylidiidæ.—*Dipylidium caninum* is a common parasite of the dog and is only occasionally found in the human being, most frequently in young children. The segments leave the rectum of the dog spontaneously and creep about so that they eventually get into the fur, where they dry and disintegrate. The oncospheres may then be taken up by the dog louse, *Trichodectes canis*, or by fleas, *Ctenocephalus canis*, and *Pulex irritans*, in which they develop into cysticercoid larvæ. Dogs become infected by biting at the ectoparasites in their fur. Transmission to the human is perhaps accomplished when dogs lick the face, hands, or tableware, or through food into which infected fleas have fallen.

Hymenolepididæ.—*Hymenolepsis nana*, or the "dwarf tapeworm," is very common in Sicily and parts of Italy, and is apparently also very widely distributed throughout the world, being reported from North and South America, and various parts of Europe and Asia. It is probably the most common of the species of tapeworms occurring in the United States. Notwithstanding its small size, its presence in large numbers may cause rather pronounced symptoms, such as loss of appetite, diarrhea, and nervous manifestations, all of which disappear with the expulsion of the parasites.

Hymenolepis murina, which is anatomically identical with *Hymenolepsis nana*, occurs in rats. According to Grassi, development may be completed without an intermediate host. Larval forms of the worm which are embedded in the intestinal mucosa grow rapidly into adult tapeworms. It is sometimes stated that cysticercoids of this species occur in the rat

flea, *Ceratophyllus fasciatus*, but the massive infection which takes place in rats following the ingestion of *H. murina* ova shows that no intermediate host is necessary, and the larval forms in the flea are probably of another species. Since there is convincing evidence that the development of *H. nana* in the human being is similarly direct, measures should be taken, especially in children, to prevent auto-infestation through the transfer of ova to the mouth on soiled fingers.

Hymenolepis diminuta, a larger species that occurs commonly in rats and mice, has in a small number of cases been seen in the human being. The larvæ are found in cockroaches, fleas, and various other insects.

Davaineidæ.—Worms of the family Davaineidæ have rarely been reported in man.

Tæniidæ.—*Tænia solium.*—The adult form of the species, *Tænia solium*, occurs only in the human being. Its larval stage, *Cysticercus cellulosæ*, exists normally in the striated muscles of the domestic pig, but is known to be present also in the wild boar, the stag, dog, cat, brown bear, monkey, and, not infrequently, in man. The cysticercus which develops in the pig is an ellipsoidal vesicle 6 to 20 mm. in length and 5 to 10 mm. in width, in the wall of which an invaginated or protruded head develops. The human being acquires the parasite by eating "measly pork" which has not been cooked sufficiently to kill the larvæ. The danger of this species to the human being is not so much due to the presence in the alimentary canal of the adult worm, as to the invasion of the tissues by its larval forms. The latter may be acquired by the ingestion of oncospheres from human feces contaminating the hands or articles of food. It is thought that auto-infection may also take place not only by contamination of the hands with oncospheres, but by the regurgitation of mature segments into the stomach during vomiting. Under such conditions the oncospheres might develop just as though they had been ingested. Since an individual harboring the pork tapeworm is, therefore, a menace both to himself and to others, measures should be taken to destroy all parasites evacuated with the stools. Personal cleanliness should be insisted upon. The transmission of the worm from the human being to pigs is undoubtedly facilitated by allowing the animals free access to privies, a custom which prevails in various parts of the world.

This species is rare in North America and most disturbances ascribed to it are probably caused by *Tænia saginata*. Stiles found only one *Tænia solium* in several hundred human tapeworms. In Portugal, however, it is more common than the "beef" tapeworm, and in South America it also occurs frequently. This parasite is seen most often in countries where pork products are eaten raw or insufficiently cooked. It has become less common in North and East Germany on account of the precautions against trichiniasis; regulations have been enforced which, although they do not prevent the selling of measly meat as such, require that it be thoroughly cooked before it is placed upon the market. If badly infested, meat is used for industrial purposes rather than for food.

Tænia solium, the so-called "pork tapeworm," measures about 2 or 3 meters in length and occasionally more. The head is globular and its rostellum is armed with a double circlet of about 26 or 28 hooks. The neck is rather thin and long. The proglottides, which number from 800 to 900, increase in size very gradually. The genital pores are situated

at the lateral margin a little behind the middle of the segment and alternate fairly evenly. Mature segments measure from 10 to 12 mm. in length and 5 to 6 mm. in breadth. Each contains a uterus consisting of a median trunk with from seven to ten lateral branches on either side, some of which are again ramified. The eggs are spheroidal and covered with an outer shell which is thin and delicate, and a thick embryonal shell with radial striations. They are between 31 and 36 micra in diameter. The oncospheres, which are each provided with six hooks, have a diameter of about 20 micra.

Cysticercus cellulosæ, the larval form of *Tænia solium*, has been found in practically all the organs of the human body. It most frequently enters the brain, and then, in order of frequency, the eye, the muscular system, the heart, subcutaneous tissue, liver, lungs, and abdominal cavity. Some individuals harbor only a single parasite, while others may be infested with thousands. Males are most frequently attacked, and constitute from 60 to 65 per cent. of patients.

The disturbances caused by these parasites vary according to their location in the body. When situated in the meninges their effect is similar to that of tumors. In the eye, they not only interfere with vision, but, because they are extremely difficult to remove, usually destroy sight.

Tænia saginata, or the "beef tapeworm," lives in the adult state only in the human intestine; its larval form, *Cysticercus bovis*, is found almost exclusively in the ox. As the cyst occurs more frequently in the pterygoid muscles than elsewhere, it may be readily overlooked. This is a common tapeworm of man and is widely distributed throughout the world, being absent only from regions where beef is not utilized as food. Since the cysticerci of this species are killed by brief exposure to low temperatures, cold storage is effective in the eradication of this worm. Ransom has found that exposure to 14° to 15° C. for four or five hours is sufficient to destroy *Cysticercus bovis*. This parasite is usually destroyed in cooking, escaping only in uncooked portions of meat or when raw beef is employed as food.

The adult worms may attain a length of 10 meters or more, even 36 meters in some instances. The head is somewhat cuboidal in shape and is unarmed. The four suckers are hemispherical; in place of a rostellum there is a sucker-like organ. The neck is moderately long and about half as wide as the head. The genital pores, which alternate irregularly, are situated somewhat behind the middle of the lateral border of the segment. The mature detached proglottid resembles a pumpkin seed and measures from 16 to 26 mm. in length by 4 to 7 mm. in breadth. The uterus has from 20 to 35 branches on each side of the median trunk, each of which may ramify further. The eggs are globular, the outer layer often remaining intact and showing one or two filaments. The embryonal shell is ovoid, radially striated, thinner than that of *Tænia solium*, and lined with a thick hyaline layer. In the cysticercus or larval stage these worms measure from 7.5 to 9 mm. in length and 5.5 mm. in breath, and consist of a vesicle with a single scolex.

Symptoms.—The disturbances associated with the presence of adult *"pork," "beef,"* and *"broad" tapeworms* in the intestine are so similar that they may be discussed collectively. There is often a sense of pressure and localized discomfort, which may shift from place to place in the abdomen, frequently associated with colicky pains. Such abnormalities of

appetite and *digestion* as morbid hunger, irregular appetite, nausea, and vomiting are common. On account of the proclivity of the proglottides of *Tænia saginata* to wander out through the anal opening, a person harboring this parasite does not usually remain long ignorant of the fact, but this is not true of *Tænia solium*, for with this species there is no active migration of the segments. Constipation or diarrhea may lead to the diagnosis of other intestinal disorders. In countries where *Tænia saginata* is common, intestinal crises with colic and pain in the region of the appendix are observed. On the spontaneous discharge of a chain of segments in the stool such symptoms immediately disappear. In addition to general intestinal disturbances a severe type of *anemia* may develop, probably because of the absorption of toxic substances produced by the disintegration of segments within the intestine. This anemia is more frequently encountered in association with the "broad" tapeworm, *Diphyllobothrium latum*, than with other tapeworms.

Treatment may be specific or symptomatic. The latter type is suitable for elderly patients and for those weakened by disease, surgical operation, heart failure, carcinoma, pregnancy, etc. Young children also should receive less radical treatment than the adult.

The difficulty in expelling tapeworms is indicated by the multiplicity of remedies advocated. Of the three large tapeworms, *Tænia solium* is the most easily expelled, then *Diphyllobothrium latum*, while *Tænia saginata* is the most refractory. In specific treatment the aim should be to recover the entire worm, including the head, for if this remains behind the segments will after a time reappear. Before administration of the anthelminthic, the bowel should be emptied of dense fecal masses. Less stress is now laid on complete cleansing of the intestine, because it frequently produces undue discomfort and even appears at times to bring about serious results. The following treatment may be employed when there are no complications:

The night before the administration of the vermifuge the patient receives no food except a cup of soup or a glass of milk, and is then given a mild laxative or an enema. On the following morning a cup of black coffee or tea should be given without anything else, to be followed half an hour later by the vermifuge. *Male fern* appears to be quite satisfactory, but success depends upon the care with which it is collected and prepared. This is much more active if collected at certain seasons; the extract should be prepared from fresh roots only. Considerable emphasis is laid by some authors on its preparation according to the exact procedure prescribed by the Pharmacopeia. *Extract. filicis maris æther* may be given to adults in capsules, in doses of 10, 12, or 15 gm.: larger doses are considered unsafe because of the serious toxic effects that may ensue. That the drug becomes toxic when administered with aperient oils (castor oil) is quite generally believed, and it is probably safer to employ a saline cathartic, such as Epsom salts, to effect the discharge of the worm. These may be given about half an hour after the male fern is taken.

The patient should be kept in bed throughout treatment. With appearance of the first segments a receptacle of warm water should be provided in order to facilitate passage of the worm and prevent separation of the chain of segments from the head portion. Unless the scolex is obtained the treatment may be unsuccessful and the patient must be re-examined after one or two months. It should always be remembered that more than one broad tapeworm may occur in a single individual. For children, pumpkin seed (*Semina cucurbitæ maximæ*) is preferable to male fern; 60 to 100 seeds may be ground with sugar, and administered in a single dose. This is to be followed within half an hour by a laxative.

Hymenolepis nana is readily expelled by oil of chenopodium (given as

for round worms). Other species of fern from Sweden (*Aspidium spinulosum* and *Aspidium dilatatum*) have proved especially successful in the expulsion of tapeworms.

Echinococcus or Hydatid Disease.—Definition.—An infection caused by the larvæ of *Tænia echinococcus*.

Tænia echinococcus in its adult form lives in the small intestine of the dog, the wolf, the jackal, and other related species. The larval stage, *Echinococcus unilocularis*, occurs in the organs (chiefly in the liver and lungs) of numerous species of mammals, such as the sheep, the ox, the pig, and man. In Australia, the parasite is maintained by the prevalence of rabbits which serve as food for the dog, and as intermediate host for the parasite. The eggs of this worm are disseminated by dogs which harbor the adult forms. They are transmitted to human beings possibly when dogs lick them or eat from dishes which are later used by man, or by transference of eggs to the mouth on contaminated hands.

Tænia echinococcus, the dog tapeworm, is very minute, 2.5 to 5 or 6 mm. in length. The head is 0.3 mm. in breadth and has a double row of hooklets on the rostellum.

The echinococcus cyst or "hydatid" forms by liquefaction of the interior of an oncosphere or embryo which has invaded the tissues. It slowly attains considerable size, in the hog, 4 or 5 cm., in cattle, that of an orange, and in man, an even larger bulk. The wall of the cystic larval form is composed of an external laminated cuticle and an internal germinative or parenchymatous layer. These two layers may be recognized throughout all subsequent development in which various structures are produced by a process of invagination. The final forms are brood capsules containing a number of scolices, each of which can develop into an adult worm if ingested by the proper host, the dog.

The course of larval development, however, differs widely. In the simplest form of echinococcus cyst there are numerous brood capsules which develop by invagination of the wall of the cyst. The scolices are produced by further invagination of the wall of the brood capsule. A large mother cyst may contain many thousands of the minute brood capsules in each of which are from 2 to 30 or more scolices. When the brood capsules rupture, the scolices may be disseminated throughout the cyst as hydatid sand. In man, instead of the immediate production of brood capsules from the wall of the maternal cyst, daughter cysts form which, although somewhat smaller, are in every other respect similar to the "mother" cyst.

Daughter cysts transplanted into other animals continue to develop and give rise to brood capsules and scolices. Even the scolices themselves when similarly transplanted may undergo vesicular metamorphosis and then continue to propagate (secondary hydatids). It is obvious from the results of experimentation that the dissemination of any portion of the hydatid during operative procedures may result in the further propagation of the parasite. The development of the echinococcus cyst does not, however, always proceed normally. Sterile cysts are produced in which no brood capsules or scolices develop. The fluid contents may become absorbed and the wall infolded to form a mass of plicated hyaline laminæ. Sometimes the hydatid cyst ruptures into a serous sac or perforates into the bronchi or alimentary canal. Cases are reported of rupture of a cyst into the urinary or bile passages or even into the inferior vena cava. Finally, the hydatid cyst may undergo secondary infection and suppurate.

Tænia echinococcus is common in various regions of Europe, Iceland, Argentine, Paraguay, and Australia. In the latter country the rabbit serves as the intermediate host and man is not infrequently attacked. In Iceland, where this parasite is very prevalent, 2.3 per cent. of the inhabitants are said to harbor the echinococcus. Its occurrence in man may be due to local customs with respect to the intimate association of man and dogs, and also to a large extent to the prevalence of the parasite in dogs.

Distribution in the Body.—Hydatid cysts occur most frequently in the liver (approximately 50 per cent.). They are also found in the lungs or pleura, in the abdominal organs, and rarely in the nervous and circulatory systems.

Symptoms.—*Hydatid Cyst of the Liver.*—The liver is usually enlarged, though small cysts may cause no change in its size. When the cyst occurs near the anterior surface it forms a distinct prominence of a tense, sometimes fluctuating consistency. If the cyst develops on the posterior surface of the liver, the enlargement is chiefly upward and an area of dulness is noted in the posterior axillary line. As the cyst becomes of considerable size, the patient may complain of a dragging sensation in the hepatic region, but there are few systemic symptoms and the general condition of the patient usually remains excellent. The tumor may be palpable for years, but cause no noteworthy symptoms. When suppuration occurs, the symptoms are those of pus formation, and this condition may be associated with more or less jaundice. Perforation may occur into any of the surrounding organs.

Diagnosis.—A palpable tumor of the liver which causes no disturbance to the patient's health and strength should suggest an echinococcus cyst. Syphilis or cancer of the liver may cause some confusion in diagnosis, and a dilated gall-bladder may easily be mistaken for hydatid disease. Hydatid cyst of the right lobe may closely simulate a pleural effusion on the right side.

Hydatid Disease of Other Organs.—Echinococcus cyst of the *lung* is a less common but by no means rare condition, and, like hydatids of the liver, may exist for some time without causing serious symptoms. Sooner or later, however, they are apt to form cavities which connect with the bronchi, and portions of the cyst may be expectorated. If the cyst ruptures into the bronchus, the diagnosis is readily made by the demonstration of hooklets in the sputum. The radiographs of the unruptured cyst are usually quite characteristic, presenting a round oval shadow quite different from that of an abscess or new growth. Echinococcus cysts occasionally occur in the *kidney*, where they convert the organ into an enormous cavity resembling hydronephrosis. Hydatid cyst of the *brain* produces symptoms similar to those of brain tumor.

The diagnosis of the presence of echinococcus cyst depends upon the findings of scolices or hooklets in material obtained by operation, in sputum, or in sloughing tissue. The peculiar, hyaline, laminated membrane, characteristic of the hydatid cyst, is readily distinguished. The presence of echinococcus cysts is also determined by the complement-fixation test and by the precipitin reaction; the former, regarded as the more reliable, has been employed in large hospitals as a routine diagnostic measure when echinococcus is suspected. More recently a skin test, using fluid obtained aseptically from hydatid cysts of cattle, has proved more satisfactory. (Drew, Kellaway, and Williams.)

Treatment.—The accepted treatment for echinococcus disease is surgical. It should be borne in mind, however, in the course of all operative

procedures that the rupture of a cyst into a serous cavity may evoke serious symptoms and collapse. Furthermore, cysts that are incompletely removed or scolices which escape from them may continue to develop. Thus, operative procedures may also serve to disseminate the disease. The *x*-ray has been employed to favor absorption of hydatids, but the value of this form of treatment has not yet been definitely established.

Tænia Multilocularis.—Echinococcus multilocularis, or *Echinococcus alveolaris,* is now shown to be a species distinct from the unilocular echinococcus, since specific differences have been demonstrated in the two types of adult tapeworms which develop in dogs. The length of the body, the number and size of the hooklets, and the shape of the uterus are dissimilar in the two species. Differences also exist in the larval stages and the geographical distribution is not the same. The mass may attain the size of a child's head, and consists of a collection of small cysts which measure from 1.5 to several millimeters in diameter. These are embedded in a soft connective-tissue stroma, so that the cut surface has the appearance of a honeycomb. It is said that hydatid cysts of this type occur in shepherds, whereas those of the unilocular type develop in individuals who care for cattle. The fact that in cattle the larval stage of *Tænia echinococcus* may somewhat resemble the multilocular hydatid has caused confusion, but definite differences between the two have been found. *Tænia multilocularis* is geographically restricted to foci in southern Bavaria, the Tyrol, Wurtemburg, northern Switzerland, Russia, and Siberia. The prognosis for patients with multilocular hydatids is even less favorable than for those with unilocular cysts. Neither therapeutic measures nor surgical treatment have proved effective. Extensive resection of the liver has been followed by recovery in one case reported by Bruns.

Tænia confusa and *Tænia hominis* are rare tapeworms, the life-cycles of which are unknown.

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DISEASES CAUSED BY NEMATODES (ROUND WORMS)

Nemathelminthes (round worms) are distinguished from Platyhelminthes (flat worms) by their form and by the possession of a body cavity in which the gut or other organs are suspended. The class Nematoda includes those with an alimentary canal. They are filiform or fusiform in shape and vary greatly in size, certain species being no more than 1 mm. long, others growing to 80 cm. or even 1 meter in length. Upon the surface, which is smooth or annulated, there may be papillæ, bristles, or alar appendages. The anterior end is often slender, while the posterior extremity is thicker and may be rounded or pointed. The sexes are usually distinct

and are readily distinguished. The male is smaller and may have a recurved posterior extremity, or, in many species, a special copulatory apparatus, such as spicules, bursæ, etc. The females are larger, not recurved, and have a genital tract which opens on the ventral surface, usually in the middle portion of the body. Not all nematodes are parasitic, for many different species are found in decaying vegetable material, in the soil, and in fresh and salt water. Certain species live as parasites on plants.

RHABDIASIDÆ

Strongyloides stercoralis (Bavay, 1877) is a very small species and, being colorless, is found only by microscopical examination. There are two distinct generations of this worm, one which lives in the mucosa of the upper portion of the small intestine, the other which lives outside the body. Only one adult form of the parasitic generation is known. This measures 2.2 mm. in length by 0.034 to 0.07 mm. in thickness. While Leuckart considered this form to be hermaphroditic, others regard it as a female, the ova of which develop parthenogenetically. The eggs are found only rarely in the stools, but being deposited in the mucosa hatch out small worms from 0.2 to 0.25 mm. in length which, after growing for a time, pass out in the feces.

Strongyloides stercoralis was formerly supposed to cause a definite disease, the so-called Cochin-China diarrhea. However, as many normal individuals harbor this parasite, its pathogenicity is probably very slight.

This species is difficult to expel, although both thymol and male fern appear to be somewhat effective. Cure is also claimed by treatment with chenopodium.

DRACUNCULIDÆ

Dracunculus medinensis (Velsch, 1674).—The female of this species, which is commonly known as the "Medina worm" or "Guinea worm," attains a length of from 15 to 80 cm. or even more, and measures from 1.5 to 1.7 mm. in thickness. This parasite is very common in certain parts of Africa and the East Indies. A few cases have been reported in the United States. The Guinea worm appears in superficial ulcerations, usually on the lower extremities, but less frequently also on the trunk, the upper extremities, eyelids, tongue, and various parts of the body. Several worms may occur in one individual. It appears at definite times of the year, usually from June to August. An intermediate host is necessary for the completion of the life-cycle of this worm. The worm is usually situated beneath the skin, where it is readily palpated and frequently outlined by a sinuous, linear elevation. The position of dead or calcified worms may be demonstrated by the *x*-ray. Preparatory to the discharge of its young, a nodule develops in the skin, upon the surface of which a vesicle soon appears, and ulceration follows. A small opening may be apparent at the base of the ulcer from which the head end of the worm may project. On moistening the ulcer with water a portion of the uterus prolapses from the worm and a milky fluid escapes which, examined microscopically, shows great numbers of small embryos with attenuated caudal extremities. The young worms upon being discharged into water move about actively for several days. They develop further when ingested by a fresh-water copepod, *Cyclops coronatus*. After migrating to the body cavity of cyclops the young worms undergo further development and moult twice. The larvæ now develop no further unless taken into the stomach. It appears probable that a full year

is required for this worm to complete its development, for the adults make their appearance only at a given season of the year, *i. e.*, in certain regions in June.

Symptoms.—The presence of this worm in the body may produce urticarial eruptions, fever, and more or less prostration. The acute symptoms, however, last only for a few days before the worms appear in the skin lesions. In case the worm is ruptured in an attempt to extract it from the tissues, serious infection may result. There is usually a marked eosinophilia present—from 10 to 50 per cent.

Treatment.—The native method of extraction of this worm consists in gradually rolling the worm around a small stick, the process continuing over a period of about a fortnight. Medical men have injected chloroform, corrosive sublimate, and other substances into the worm. The parasite is removed more easily after it has discharged its embryos, a process which may be hastened by frequently moistening the ulcer with cold water. The use of boiled water for drinking and culinary purposes is probably the only really effective prophylactic measure.

FILARIASIS

Definition.—A disease caused by infection with *Filaria bancrofti* (Cobbold, 1877). The adults are thread-like. The female measures from 50 to 65 mm. long by 1.5 to 2 mm. broad. The male measures 25 to 30 mm. in length by 0.1 mm. in thickness. The tail is recurved and there are two spicules of unequal length present.

The adult forms of this parasite live in the lymphatics, in lymph-follicles, and in various organs, such as testis, epididymis, spermatic cord, in mammary cysts, and in abscesses in various parts of the body. Dead and calcified worms are found in some instances. The embryos, or microfilariæ, occur in the blood-vessels, but their appearance in the peripheral circulation is periodical, occurring in large numbers only during the night, and nearly but not quite disappearing during the day. This periodicity may be reversed if the patient sleeps during the daytime. In certain countries, however, it appears that the larvæ of *Filaria bancrofti* show no periodicity, and it is suggested that in such localities day-biting mosquitoes are concerned in their transmission.

Life History.—A large number of species of both anopheline as well as culicine mosquitoes serve as intermediate hosts for *F. bancrofti*. After being taken with blood into the stomach of the mosquito the microfilariæ cast their sheath after a short time, and then penetrate to the thoracic muscles, where they proceed to develop into thick stumpy forms. After a second moult the larva grows to about 1.5 mm. in length and eventually migrates from the thorax to the labium. While the mosquito is drawing blood from a patient the larvæ escape through Dutton's membrane, which stretches between the labella where they fork at the end of the labium, to the surface of the skin, which they penetrate. Their subsequent development in the human body is probably a long one, since children do not show the infection until they are at least four or five years old.

Incidence.—This parasite is widely distributed, but is particularly common in tropical countries. Cases of filariasis have been reported in the southern part of the United States by Matas, Opie, and others.

Symptoms.—The nature of the symptoms depends not only upon the lo-

cation of the lesions, but on the degree of infestation. The parasite may produce a lymphangitis which is associated with high fever, enlargement of the lymphatic glands, and inflammatory swelling of the parts affected. After repeated attacks, permanent thickening of the tissue takes place. When lymphangitis occurs in the legs, marked swelling sometimes follows, and a condition known as *elephantiasis* occurs. Sometimes the scrotum is involved and reaches enormous size.

Chyluria.—One of the most striking symptoms of filariasis is chyluria. From time to time the patient passes white, opaque urine which resembles milk. Sometimes the chylous fluid contains blood which gives it a slightly reddish color. This condition is caused by dilatation and rupture of lymphatic vessels in some part of the urinary tract. Microscopically, the urine contains minute fat globules and red blood-cells.

Diagnosis.—Demonstration of the larva in the blood, urine, or chylous fluid establishes the diagnosis. Most cases show an eosinophilia. According to Osler, neither chyluria nor elephantiasis are pathognomonic, as both of these conditions may occur in a non-parasitic form.

Treatment.—There is no specific treatment for filariasis, although some of the newer arsenicals are reported to have had a beneficial action. In countries where the disease is prevalent the inhabitants should be well protected from mosquitoes. The chyluria is usually relieved by the avoidance of all fat in the diet. Elephantiasis is a very difficult condition to treat. The patient should be at rest, with the legs elevated and firmly bandaged. When the scrotum is involved it may be successfully treated by surgical removal of the redundant tissue.

Filaria (*demarquayi*) *ozzardi*, Manson, 1895, occurs in the West Indies and northern South America. The adults occur in the mesentery and the microfilariæ in the circulating blood are without sheaths.

Loa loa, Guyot, 1778 (*Filaria oculi*), which occurs in the adult stage beneath the conjunctivæ and beneath the skin, is very readily extracted through a small incision. The microfilariæ present a definite sheath and are difficult to differentiate from those of *F. bancrofti*. The fully developed larvæ have been found in the salivary glands of a biting fly of the genus *Chrysops*, as shown by Leiper. Other species of the *filariidæ* are *Acanthocheilonema perstans*, Mason, 1891; *Dirofilaria magathæsi*, R. Blanchard, 1895; *Onchocerca volvulus*, Diesing, 1841.

TRICHOTRACHELLIDÆ

Trichuris trichiura, Linnæus, 1761 (*Trichocephalus dispar*, etc.), or whip worm, is of no great importance in human pathology. Occurring in the appendix, it may occasionally excite inflammation, and when occurring in enormous numbers in the cecum it may occasionally be associated with serious symptoms, or, in rare instances, cause death. The anterior portion of the body of both male and female is greatly attenuated, and this portion is threaded beneath the epithelium of the intestine, while the thicker portion of the body hangs free. The male measures from 40 to 45 mm. and the female from 45 to 50 mm. in length. The posterior extremity of the male is recurved and shows a long spicule. The eggs are barrel-shaped and have a thick brownish shell with a large albuminous plug at each end. The species is widely distributed throughout the world, and occurs not only in thickly populated, but in rural districts as well. This species is very resistant to the more common anthelmintics, but is expelled by the fresh latex of *Ficus*

glabrata which grows in Colombia, S. A. This is practically non-toxic so that doses of 40 to 50 grams are administered to adults.

TRICHINIASIS

Definition.—A disease produced by *Trichinella spiralis*. The adults live in the small intestine, while the young worms pass from the intestines to the voluntary muscles, where they become encapsulated.

Trichinella spiralis (Owen, 1835).—Both males and females are slender worms; the former measure 1.4 to 1.6 mm., the latter from 3 to 4 mm. in length. The female shows a slender anterior extremity with a bluntly rounded posterior extremity. This species is ovoviviparous and the young worms continue to develop in the host occupied by the adults. The latter occur in the mucosa of the small intestine and the embryos escape directly into the tissues, and either pass through the lymphatics to the blood-stream, or may migrate actively through the tissues, since they are found in considerable numbers in serous spaces, such as the peritoneal and pleural cavities. The dissemination of the larvæ appears to be largely passive and they are carried in the blood-stream to all parts of the body. Further development, however, only takes place in the skeletal muscles which are penetrated by the small worms. After penetrating the muscle-fiber the worm grows rapidly, and in the course of two or three weeks becomes coiled. The lemon-shaped cyst is subsequently formed about the larval worm. This usually encloses nuclei and cytoplasm derived from the degenerated muscle-fiber. The fully developed larvæ now become quiescent and persist for many years. Small areas of adipose tissue appear at the poles of the cysts in the place of the degenerated muscle-fibers. In some instances, calcification occurs, and, beginning at the poles of the cyst, may increase to such an extent that the worm is eventually destroyed. Newly formed cysts are practically invisible, but under the most favorable conditions give an appearance of very fine sand embedded in the surface of the muscle. After calcification has taken place they appear as minute opaque points in the muscle. Their average measurement is 0.4 mm. in length and 0.25 mm. in breadth.

There is no further development of the worm after encystment until the flesh is eaten by another animal. After the digestion of the cyst wall the liberated worm becomes sexually mature in a few days, and in from four to seven days after ingestion the females show fully developed embryos. The latter on being discharged require several days to penetrate the skeletal muscles, for they are rarely found in the latter before the tenth day after the ingestion of trichinous muscle. The adult worms are said to persist in the human intestine for five to seven weeks after the ingestion of trichinous meat. Some observers claim to have found them after eleven and twelve weeks. It is said that the males, after copulation has taken place, tend to die off, but in the rat, the male trichinellæ persist as long as the female, both disappearing from the animal in from three to four weeks. Many experiments have been performed in order to determine whether this species is transmitted by the contamination of food with intestinal contents. With the exception of the results obtained in a comparatively recent investigation (see Raebiger, quoted by Nicoll) all attempts to produce infection in this manner have failed. Apparently both the adult worm and the embryo are unable to withstand gastric digestion. The parasite is practically always

acquired by the human being through the ingestion of trichinous meat, and this also probably holds true in general with respect to its transmission in other species. Encysted trichinæ are killed by heating to 55° C., so that the temperature of 58.33° C., required by the United States Bureau of Animal Industry, as the minimum temperature at which pork products must be cooked in establishments operating under federal inspection, is evidently effective (Ransom and Schwartz).

Infection.—*Trichinella spiralis* occurs most frequently in the gray and in the black rat. The parasite is acquired by the human being through eating raw or improperly cooked pork. Its occurrence in the pig, although not rare, is much less frequent than in rats. For example, in inspections made by the Prussian Government between the years 1878 and 1902 it is shown that from 1 pig in about 2000 to 1 in somewhat over 12,000 pigs infection is found. The feeding of infected meat of dead animals to pigs is probably a factor in the maintenance of this disease. The prevalence of the disease obviously is dependent upon local custom with respect to eating raw or partially cooked pork products.

Morbid Anatomy.—This consists chiefly of a general myositis. Following the invasion of a muscle-fiber with the small worm, the cross striations for the most part disappear and the nuclei become enlarged and appear to multiply. Occasional vestiges of the striations are apparent near such nuclei. In the course of two or three weeks after the onset of the disease, the invaded muscle-fibers become spindle-shaped about the worm, which at this time is beginning to become definitely coiled. The capsule within which the worm is eventually encysted encloses the remains of the degenerated muscle-fiber in which the nuclei remain apparent for a considerable period of time. Inflammatory changes occur in adjoining muscle-fibers which have not been invaded, and there is increase in the interfibrillar connective tissue. After the trichina larvæ have become encysted, groups of fat cells appear at the poles of the cyst, and later on calcification of the latter may occur.

In a febrile disturbance with such pronounced symptoms it is natural to assume that a toxin is produced, and this is quite generally conceded. The toxin, however, is not readily demonstrated by experiment, for the adult worms may be collected in large numbers and, after grinding, be injected directly into the vein of a mouse without producing any pronounced symptom. Certain investigators have obtained results indicating that toxic substances are produced as the result of the rapid degeneration of skeletal muscle which follows the invasion of the worm. Practically no immunity is conferred by an attack of trichiniasis, second and even third attacks having been recorded. In experimental animals the infiltration about the larval worm during encystment is somewhat more marked in second or third infections with this parasite.

Symptoms.—In trichiniasis the symptoms depend in large part upon the number of parasites eaten. When only a limited number are ingested, the few embryos which may reach the muscles cause little, if any, reaction in the patient. On the other hand, when large numbers are eaten severe symptoms and death may follow. A typical case is characterized by the presence of digestive disturbances, muscular tenderness, and continuous fever. The disease may be divided into two periods, as follows: (1) *the period of invasion,* which includes the first week after the ingestion of tri-

chinous pork. During this period the worms are developing in the intestinal tract. There may be nausea and vomiting and watery diarrhea. Periodical abdominal pains may appear at the end of this time, and embryos occur in great numbers in the serous cavities; (2), *the period of dissemination*, which begins about the eighth or tenth day. Migration of the parasites into the muscles excites more or less myositis, which is evidenced by muscular tenderness. This tenderness is most marked in the muscles of the extremities, particularly the gastrocnemii. The muscles of mastication, speech, and respiration may also be involved, and dyspnea may be a prominent symptom. The temperature varies with the severity of the attack, sometimes reaching 104° or 105° F., and maintaining a plateau quite suggestive of typhoid fever. A characteristic feature is edema of the face, particularly around the eyes. Later it may also occur in the extremities, when the involvement of the muscles is most marked.

As the disease progresses, the patient becomes cachectic and anemic. At this time there may be delirium or somnolence, and secondary infection such as pleurisy or pneumonia may occur. Furunculosis is not an uncommon complication.

The blood shows a marked leukocytosis which may reach 30,000. The characteristic feature of the blood-count is an eosinophilia which often reaches 50 per cent. or even more.

The duration of the disease depends entirely upon the severity of the infection. The milder cases run a short course of ten to twelve days, while severe infections may continue to have symptoms for six to eight weeks.

Diagnosis.—The disease may be confused with acute arthritis and with typhoid fever. The diagnosis is made certain by finding the larvæ in a bit of excised muscle, or in samples of the pork which the patient has eaten. The diagnosis may also be based on the presence of a marked eosinophilia together with fever and tenderness of the muscles. It is probable that mild infections frequently pass unrecognized.

Prognosis.—The death rate in trichiniasis ranges from 2 to 3 per cent. The prognosis depends upon the number of larvæ in the trichinous pork eaten. Early diarrhea is a favorable symptom, as it frees the patient of a considerable number of embryos.

Treatment.—The most satisfactory prophylactic treatment is the complete cooking of pork and sausages. In handling a case of trichiniasis the first indication is to thoroughly evacuate the gastro-intestinal tract. Calomel or castor oil should be given at once and followed a few hours later by magnesium sulphate. Colon irrigations are also of value. Various vermifuges have been recommended and glycerin has been used for the purpose of destroying the worms by its hygroscopic action. When the parasites have invaded the muscles there is no known method of attacking them successfully. Grove has recently reported favorable results from the injection, during the period of invasion, of antimony potassium tartrate. One cubic centimeter of a 2 per cent. solution is first injected, then 2 and 3 c.c. on successive following days, and finally, after an interval of two days, a dose of 4 c.c.

DIOCTOPHYMIDÆ

Dioctophyme renale (Gmelin, 1789).—This worm is of a bright red color, almost blood red. The males measure up to 40 cm. in length by 0.6 cm. in thickness. The posterior extremity is transversely truncated and provided

with a collar-like bursa. The spicule measures from 5 to 6 mm. in length. The females may measure as much as 100 cm. in length by 1.2 cm. in thickness. The eggs are ovoid with a thick shell showing numerous pit-like depressions in the outer surface. The habitat is the pelvis of the kidney, occasionally the peritoneal cavity, of the dog, wolf, fox, seal, otter, mink, marten, pole-cat, horse, and occasionally man.

In many cases in which this worm has been reported in man it has been confused with other species, but there is a small series of apparently authentic cases of its occurrence in man. Its mode of transmission is unknown. In the mink, the invaded kidney is reduced to a sac enclosing one, or a number of worms. This sac shows on its internal surface a stellate calcification with slender, radiating, sharp-pointed spicules. The uninvolved kidney presents a pronounced compensatory hypertrophy.

ASCARIDÆ

Ascaris lumbricoides (Linnaeus, 1758).—Fresh specimens are of pinkish or reddish-yellow color, and the body is of an elongated spindle-shape. The male measures from 15 to 25 cm. in length, about 0.3 cm. in diameter, and the posterior extremity is conical and bent forward ventrally. There are two spicules present which measure 2 mm. in length. The female measures from 20 to 40 cm. in length and about 0.5 cm. in thickness. The eggs are ellipsoidal, with a thick transparent shell covered with an albuminous layer which is characteristically mammillated. The eggs measure from 50 to 70 micra in length by 40 to 50 micra in breadth. They are deposited before segmentation and acquire a yellowish or deep brown color due to the staining of the albuminous layer with bile. Abnormal or unfertilized eggs are also frequently found. They are distinguished by their somewhat greater length and their truncated extremities, giving them a somewhat quadrilateral outline.

Ascaris lumbricoides is one of the most frequent parasites of man, and is distributed throughout all parts of the world, although considerably more prevalent in warm climates. It occurs more frequently in children than in adults, and more commonly in rural districts than in cities. A variety of this species occurs in the domestic pig. A considerable period of time is necessary, usually about one month, under favorable conditions for the embryo to develop in the egg after its discharge from the body. The development of the adult worm has followed the ingestion of such ripe eggs, and it has generally been assumed that the development of the worm occurred in the intestine. The investigations of Stewart and of Ransom and Foster have shown that larval forms of the pig ascaris pass from the alimentary tract through the tissues, and possibly to some extent through the circulation, so that they appear first in the liver and later in the lungs. They subsequently follow a route similar to that of the hookworm, so that after reaching the lung they escape into the air passages and are swallowed by the host, to undergo further development in the intestine. A few pass from the lung into the circulation and are distributed to other parts of the body. Koina infected himself experimentally by swallowing ripe ascaris eggs and developed symptoms of lung involvement with larvæ in the sputum. Later on, following an anthelmintic, a large number of adult ascaris were recovered.

The *pathogenicity* of this worm is very slight, and in many cases its

presence is unsuspected. When occurring in great numbers it may produce intestinal obstruction, or when complicated by febrile disturbances it may wander to unusual parts of the body, as, for example, the stomach, esophagus, nose, air passages, and the bile-ducts. The obstruction of the latter may be followed by abscess, and terminate in death. These worms may also escape into the peritoneal cavity through gunshot wounds of the intestine, through typhoid ulcers and ruptured appendices, and have also been found in many other unusual sites.

Ascarides of lower animals, such as those of the dog and cat, occur but rarely in the human being.

Treatment.—Both santonin and chenopodium have served as specifics for the removal of Ascaris, but the use of the former should be abandoned, as it is more toxic and less effective than other available vermifuges. Ascaridol, the active principal of oil of chenopodium is to be preferred, but if not obtainable, the latter drug, which contains at least 70 per cent. of the active principal, may be employed. The adult dose is 1 c.c. on an empty stomach, followed in one hour by a purge of magnesium sulphate. For children, the drug may be mixed with castor oil and given in doses of 0.1 c.c. for each year of age. Carbon tetrachlorid is less effective, but may be used with the oil of chenopodium in the proportion of 2 to 1 for adults.

OXYURIDÆ

Enterobius (*Oxyuris*) *vermicularis* (Linnæus, 1767) (*"Pin worm"*).—Color, whitish. The male measures from 3 to 5 mm. in length and shows a pronounced curvature of the posterior extremity of the body. The female measures about 10 mm. in length and is nearly straight and of fusiform shape with attenuated posterior extremity. The eggs are oval, asymmetrical, with double-contoured, colorless shells, and measure 50 to 55 by 16 to 25 micra. The ova contain a fully developed, tadpole-like embryo. Its habitat is the large intestine of man.

The *pin-worm* occurs chiefly in children and is of some pathological importance. The adult worms may crawl from the anal opening and produce considerable itching and irritation between the nates and on the perineum. In females they may invade the genitalia and there produce considerable irritation. In rare instances they may pass through the uterus and tubes and reach the peritoneal cavity. This species is peculiar in that it is possible for reinfestation to take place. The eggs containing fully developed embryos may reinfest the individual from which they are derived. Children are prone to get the ova on the fingers through scratching, and so transfer them to their mouths. Riley has reported *Syphacia obvelata*, an oxyurid of the mouse, in the human being.

Treatment.—Chenopodium may be administered as outlined above, or a capsule containing santonin 0.05 gram, calomel 0.10 gram, is given each morning for three days. Enemas are given for the purpose both of removing worms from the large bowel and of preventing reinfestation. It is especially important in children to alleviate local pruritus, and with small children to provide such clothing as to prevent the contamination of the fingers.

STRONGYLIDÆ

The family *Strongylidæ* includes the subfamily *Metastrongylinæ*, Leiper, 1908; *Trichostrongylinæ*, Leiper, 1908; and *Ancylostominæ*, Railliet, 1909.

The last of these is the most important with reference to human disease. The *Ancylostominæ* are further divided into two groups—*Œsophagostomeæ*, Railliet and Henry, 1909; and *Ancylostomeæ*, Railliet and Henry, 1909. Worms of the genus *Œsophagostomum* occur in apes, monkeys, and various other animals, but apparently very rarely in man. They produce cysts within the submucosa of the intestine which, projecting inward, appear as tumor-like masses.

The group *Ancylostomeæ* includes the "hookworms," of which *Ancylostoma duodenale*, Dubini, 1843, and *Necator americanus*, Stiles, 1902, are the most important clinically.

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UNCINARIASIS

(*Ankylostomiasis, Hookworm Disease, Miner's Anemia, Tunnel Worker's Anemia, Tropical Chlorosis, Egyptian Chlorosis*).

Definition.—A disease due to infection with certain metazoan parasites (*Ankylostoma duodenale* or *Uncinaria americana*) and characterized by varying degrees of anemia and the results thereof.

History.—There is no doubt that hookworm disease has existed for thousands of years. It was confused with other diseases until the specific cause was first found by Dubini in 1838, who found the worms in autopsies and gave them the name Anchylostoma, meaning "bent mouth." Bilharz in 1853 and Griesinger in 1854 recognized the relation of hookworms to the extremely prevalent and often fatal Egyptian chlorosis. Grassi and Parona in 1877 recognized the diagnostic value of the ova in the feces. The great prevalence of hookworm disease in the workers in the St. Gothard tunnel in 1879–80 attracted much attention.

Allen J. Smith in 1895 found hookworm ova in feces from a water-closet in Galveston, Texas. In 1901 he recognized differences in the worms expelled by a patient from Australia from other known species, and Stiles later showed the existence of a new species which he called *Necator americanus*.

Stiles in 1901 showed that hookworm infection was more or less wide-spread in the United States, basing his opinion upon the fact that the cases reported by Schaeffer and others from widely separated parts of the country could be explained in no other way. For several years Stiles continued to investigate the prevalence and importance of the disease in the southern states, and it was his influence which contributed largely to the founding of the Rockefeller Hookworm Commission.

Ashford in 1899 found hookworm infection in Porto Rico. The Porto Rico Anemia Commission (Ashford, King, and Gutierrez) in 1904 showed that 90 per cent. of the natives of Porto Rico were infected and that this was the cause of the prevalent anemia in that country.

Looss in 1898 made the important discovery that infection takes place through the skin. This was later confirmed by Schaudin and others. Information as to the mode of infection made possible the working out of control measures which have now been carried to all parts of the world.

Incidence.—Uncinariasis is widely distributed throughout the world, in a belt encircling the globe from about 38° N. latitude to 35° S. latitude. It is a disease of warm countries, being most prevalent as the equator is approached. Wherever there is a warm climate and plenty of rain hookworm disease is found in the poorer, less civilized classes of people. It is largely a disease of the rural population, especially in countries like the southern states, where there is almost none in towns and cities. In other countries where the economic condition of the poorer people is low and where the state of civilization is not so high, it occurs everywhere, but to a much less degree, of course, in the cities. The infection rate in large parts of many countries is almost 100 per cent. Vast areas containing millions of people, in India, China, Malay States, Africa, Porto Rico, Central and South American countries, West Indies and other countries, have an infection rate for all the people of 60, 70, or 80 per cent. In Europe it is chiefly a disease of miners in Germany, Hungary, France, and Belgium.

Darling found among Malays a higher percentage of males infected than females, and also larger numbers of worms in men than in women, boys, or girls. Men and women are infected less often than children in the United States.

Etiology.—Two species of hookworms infect man—*Ankylostoma duodenale*, prevalent in European and in many Asiatic countries, and *Uncinaria americana* (*Necator americanus*), prevalent in the Western Hemisphere, in Africa, and in many other parts of the world. The general appearance of both species is practically the same. Female ankylostomas are 12 to 18 mm. long; necators, 8 to 15 mm. Males of both species are 6 to 10 mm. long and about 0.45 mm. thick. For practical purposes there is no necessity to differentiate the two species.

When feces containing hookworm ova are deposited on the ground and become aërated under favorable conditions of shade, moisture, and temperature, they develop embryos which hatch out in from twenty-four to seventy-two hours. After about five days they become encysted and capable of infecting man upon proper exposure. Although infective larvæ have been kept alive for more than a year in the laboratory under experimental conditions, it has been shown by Augustine that under natural conditions they rapidly die out in from a few days to six or eight weeks. When mud containing these encysted larvæ comes in contact with any part of the body, the feet for example, they quickly penetrate the skin by way of the hair-follicles or sweat ducts. They possess remarkable ability for burrowing through tissue and sooner or later enter small blood-vessels. The blood-stream carries them through the heart and then to the lungs, where they lodge in the capillaries. They burrow again, and finally reach the bronchi, where they are carried upward by the outward flow of the mucus until they reach the trachea and larynx. Some may be coughed up and spit out, but others are swallowed and pass into the stomach, thence into the duodenum and jejunum. Six to eight weeks after the date of infection they begin to lay eggs, which are passed with the feces. The worms may live as long as seven, and probably as long as ten years.

Pathogenesis.—Loeb and Allen J. Smith have shown that the head-glands of the hookworm secrete a substance which retards coagulation, and Whipple has demonstrated a hemolytic poison in the parasite. The tissue

at the site of the bites is packed with eosinophils, and nature's effort to supply these as needed accounts for their increase in the blood.

The worm feeds largely upon blood, and although the amount drawn by a single worm is very small, the amount drawn by hundreds and thousands, continued day after day for months and years, is ample explanation for the anemia. This is especially true if we consider the fact that bleeding continues at the site of the bite for hours after the worm loosens his hold and moves on to another spot. Blood in small or larger amounts is demonstrable at all times in the intestinal contents of hookworm subjects. Occult blood is demonstrable in the feces even in light infections. Long-continued loss of blood and possibly a toxin are the cause of the anemia, and all the other symptoms result from it.

Morbid Anatomy.—Subjects that have died of hookworm disease show extreme anemia, usually dropsy, dilatation of the heart, serous fluid in the cavities, and the presence of enormous numbers of the worms in the duodenum and jejunum. Many of these are still attached to the mucous membrane, which is speckled with small hemorrhagic spots, the sites of previous bites. Sandwith found 250 worms and counted 575 bites in one case. Microscopically, the mucous membrane may be thinned and more or less denuded of epithelium where the greater part of the feeding took place. The tissues around recent or old bites are packed with eosinophils.

Symptoms.—The symptoms of hookworm infection vary greatly in character and in severity, depending upon the number of worms and upon other individual factors in different cases. The number of worms may vary from a single parasite to a number sufficient to kill the patient, that is, 3000 to 5000. Obviously, the symptoms produced by very large numbers of worms would be quite different from those produced by very small numbers. If a patient can survive infection with hundreds of worms, it is evident that very small numbers may produce few or no recognizable symptoms.

Most cases of infection with any considerable number of hookworms give a *history* of going barefoot and having "ground itch" at some previous time. They also give a history of residence where hookworm disease prevails, and usually of an occupation that affords exposure to infection, such as agricultural labor, mining, etc. In cases of heavy infection there is usually a history of long-standing anemia, weakness, and palpitation upon exertion. In children, there is often a history of weakness and of retarded development. Some patients admit having a capricious appetite and eating such things as dirt, coffee grounds, etc. Others, although they have acquired such habits, deny them, either from shame or from fear of chastisement.

The symptoms of *ground itch* consist of, first, a burning, stinging sensation, followed by intense itching of the feet or other parts of the body infected by the parasite. Small vesicles appear, soon followed by pustules. These may become confluent. The lesions are located between the toes or on other parts of the feet. The vesicles or pustules are usually broken by scratching and rubbing. There is considerable weeping if they are broken. Later a dry crust forms except between the toes, where there is constant moisture. The condition runs its course in about seven to ten days, after which complete recovery usually takes place.

Most if not all of the general symptoms of hookworm disease are the

result of a long-standing anemia. The anemia may vary from a very slight amount in the case of mild infections to the most severe grade, in which the hemoglobin is reduced to 15 or 20 per cent. or even lower, and the red cells fall as low as 1,000,000 per cubic millimeter. There are few such extreme cases except in those countries where the disease is very prevalent. In the southern part of the United States there are not many cases in which the hemoglobin goes below 40 or 50 per cent.

The hemoglobin is always reduced more than the cell count, giving the low color index characteristic of secondary anemia. The victim is pale, and if the disease has lasted for many years the complexion becomes sallow, giving rise to the "tallow face" of the southern states. There is no leukocytosis, but the eosinophils are increased in most cases, sometimes reaching 25 or 30 per cent.

Children who are heavily infected do not grow normally, nor is their mental development as rapid as it otherwise would be. Stunted growth is accompanied by delayed puberty, apathy, and lack of energy and physical capacity. There is a common belief that hookworms are the cause of laziness, but, as a matter of fact, the victims are weak from loss of blood and not lazy. Dyspnea and palpitation upon exertion are common, due no doubt entirely to the anemia. Dilatation of the heart and hemic murmurs are noted in severe cases. Chronic leg ulcers are often found. General edema (dropsy) often occurs in severe infections.

Hookworm disease is not a painful condition. Except perhaps for some epigastric discomfort the patient rarely complains of definite pain. There is, however, a marked hunger in many cases, and a craving for abnormal things, such as dirt, chalk, salt, starch, and hair.

It must be understood that while such symptoms as are indicated above occur in severe cases, the vast majority of patients present much milder symptoms or no actual symptoms at all. It may be impossible to demonstrate anemia when only a few worms are present. Eosinophilia may occasionally be absent even in severe cases, but it is usually present to a moderate degree even in mild infections.

Complications.—There are no special complications of hookworm disease. Since it is a disease largely of warm, damp climates and of unhygienic environment, especially soil pollution, it is often associated with the diseases peculiar to these conditions. Perhaps the most important complication is nephritis, because of the fact that damaged kidneys do not tolerate well the specific treatment for hookworms.

Diagnosis.—"The secret of the diagnosis of ankylostomiasis, like that of many other diseases, is to suspect its presence" (Manson).

The definite diagnosis of hookworm disease can be made only by finding the eggs of the worms in the feces by microscopical examination, or by finding the worms themselves in the stools following treatment. The former is by far the more practical and reliable method. Microscopical examination of the feces is so simple, and furnishes such definite information that it should always be made when hookworm disease is suspected. The ova are easily recognized, and they can practically always be found, even when the infection is mild.

The technic is simple. The preparation is made by placing a drop of water on a microscope slide and stirring in a particle of feces with a toothpick or other suitable object. The low-power lens is used for making the micro-

scopical examination. In heavy infection, many ova will be found in one such preparation. Where there are very few worms, the number of ova will be less. Examining more than one preparation increases the chances of finding ova when the infection is light. Failing to find any ova by this technic does not eliminate the possibility of the patient's having a few worms, but it does eliminate hookworm infection in sufficient numbers to cause recognizable symptoms. For instance, a case of anemia in which no hookworm ova can be found by this technic is presumably not due to hookworms.

In order to eliminate the presence of hookworms in very small numbers, special technic for concentrating the ova in the feces is of assistance. Several methods have been proposed. Concentration by means of the centrifuge is the best and most practical method. A suspension of feces in water is made, strained through two or three thicknesses of gauze, and then poured into a centrifuge tube. This is centrifuged *a few seconds only*, the length of time being determined by the speed of the particular centrifuge used. The object is to throw down the hookworm ova, but not the smaller particles in suspension. A common mistake is to centrifuge too hard and too long. The supernatant fluid is poured off and the tube is refilled with water. Shake and centrifugalize again; then pour off the supernatant fluid. Any ova present are in the bottom of the tube. Shake or jar the tube in a way to break this sediment loose from the bottom of the tube and pour it out on a slide for examination. By this method ova should always be found if the patient has even one female worm that is depositing eggs.

Hookworm disease should be suspected in the presence of any of the conditions associated with the disease, such as anemia, eosinophilia, stunted growth, etc. A history of residence where the disease is endemic should suggest it, especially if accompanied by a history of going barefoot and having attacks of ground itch. A positive diagnosis cannot be made on any or all of these, however. Whenever hookworm disease is suspected, an examination of the feces should always be made.

Prognosis.—Barring instances in which the condition of the patient is serious before specific treatment is begun, or those in which the condition is so extreme as to make the treatment itself dangerous, the prognosis of hookworm disease is always good. A positive cure of the infection can be confidently expected in every case that is properly treated.

Without treatment hookworm disease may destroy life, depending upon the amount of infection and other individual factors. The number of worms gradually diminishes unless the individual receives fresh infection. Within a period of one or two years the number is very much less, but it takes five to seven years or even longer for all worms to disappear spontaneously.

Persons whose growth has been badly stunted develop rapidly when their worms are removed by treatment, but it is doubtful if such a badly stunted person can ever attain his normal stature unless relieved before the age of twenty to twenty-four. On the other hand, if relieved of the infection before the end of the normal growing period of life, the stunted growth may be entirely overcome.

The anemia and other more or less indefinite symptoms of hookworm disease rapidly disappear following removal of the infection. The hemoglobin often jumps from 50 to 80 or 100 per cent. within a month or two after treatment is started.

Treatment.—There are three specific drugs used at the present time for the treatment of hookworm infection—thymol, oil of chenopodium, and carbon tetrachlorid. Thymol has been in use for the longest time. Each one is highly effective, one being preferred by some and another by others. Thymol is perhaps less popular than either of the other two at the present time. There are many different routine methods of carrying out the treatment with each of the remedies. Generally the treatment is repeated about once a week until all the worms are expelled. This takes from one to six or eight treatments. However, most of the worms (60 to 70 per cent. from thymol, 80 to 90 per cent. from oil of chenopodium, and 90 per cent. or more from carbon tetrachlorid) are expelled with the first treatment.

In treatment with *thymol* the best results are obtained by allowing no supper, giving a saline purgative at night, followed early the next morning by three 15-grain doses of thymol one hour apart. Two hours after the last dose of thymol another saline purgative is given to remove the thymol and prevent further absorption. The thymol may be coarsely powdered and given in capsules. Mixing the thymol with compound jalap powder, as advised by Washburn, seems to be a good plan. It acts as a purgative and obviates the necessity of the second saline.

Oil of chenopodium is more effective when there is no preliminary abstinence from food and no preliminary purge is given. Exhaustive studies of the factors controlling efficiency of chenopodium treatment were made in the Orient by Darling, Barber, and Hacker, and later in Brazil by Darling and Smillie, who reached the following conclusions:

1. A preliminary purge does not add to the efficiency of the treatment with chenopodium, when the drug is given in two doses, 1.5 c.c. being considered the adult dose.
2. A preliminary starvation period is not necessary in the treatment of hookworm disease with chenopodium in divided doses of 1.5 c.c.; on the contrary, the efficiency of the chenopodium is lessened.
3. A small amount of food given coincidently with the drug, when the chenopodium is given in divided doses of 1.5 c.c. greatly diminishes the efficiency of the drug in the treatment of hookworm disease.
4. In the smaller doses of chenopodium that are given children the decrease in efficiency of chenopodium caused by the factors of preliminary purge, starvation period, and food is much more striking than in the full adult dosage of 1.5 c.c.

Early in the morning a dose of 0.5 c.c. (8 minims) of oil of chenopodium is administered by mouth every hour until three doses have been given. Two hours after the last dose, a saline purgative (magnesium sulphate) is given. The oil may be taken in capsules by those who are able to swallow them, or it may be mixed in a little syrup or dropped in a spoonful of water.

Carbon tetrachlorid as a specific for hookworm disease was first proposed by Hall, who based his observations upon experiments on animals. Since that time it has been extensively tried by Hampton, Lambert, Smillie and Pessoa, Hill, Cooper, and many others. From present information it appears to be somewhat more effective than oil of chenopodium for hookworms, but less effective for ascarides. Although many thousands have been treated, in most instances without untoward effects, several deaths have been reported. The usual dose is 3 c.c. No fasting is necessary. One full dose seems to be as effective as several divided doses. It is followed within two hours by a saline purgative—90 to 100 per cent. of the hookworms are removed by one dose of this drug.

A combination of 2.5 c.c. of carbon tetrachlorid with 1.5 c.c. oil of

chenopodium is perhaps a more desirable treatment because it removes ascarides and sometimes other worms in addition to the hookworms.

No tonic treatment is required in hookworm disease. There is rapid recovery following the removal of the worms. Plenty of good food is needed, but rarely iron or other drugs.

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THE RELATION OF INSECTS AND OTHER ARTHROPODS TO DISEASE

In the following brief survey no attempt will be made to classify or describe the numerous species of arthropods which transmit or produce disease in the human being. Representatives of the phylum *Arthropoda* are characterized by the possession of joined appendages or limbs; respiration is effected through a system of tracheal tubes which open on the surface of the body; and the deposition of chitin in the cuticle produces a more or less rigid exo-skeleton. Included in this phylum are the classes *Arachnoidea*, arthropods without antennæ, with head and thorax fused together, and, in the adult stage, four pairs of legs; and *Insecta*, arthropods with head and thorax distinct, which possess antennæ and have only three pairs of legs.

The mites (*Sarcoptidæ*) and ticks (*Ixodidæ*) are the more important families of arachnoids from the medical point of view, while the insects are represented by the mosquitoes (*Culicidæ*), lice (*Pediculidæ*), bedbugs (*Acanthiidæ*), winged bugs (*Reduviidæ*), fleas (*Pulicidæ*), and various families of biting and non-biting flies. Although in this brief discussion of diseases either transmitted or produced by arthropods scarcely more than mention is made of the species concerned, sufficient familiarity with the anatomy to permit identification of the various arthropods, and a knowledge of their life history is of the utmost importance, for upon these facts depends the

control of certain diseases. The subject is adequately discussed in a number of books which may be consulted for further reference.

Non-parasitic Arthropods which Transmit Disease.—Non-parasitic arthropods may serve as intermediate hosts for parasites of the human being, as agents in the mechanical dissemination of pathogenic micro-organisms, or themselves, in the larval stage, play the rôle of accidental parasites. The more important non-parasitic *Arthropods* which serve as intermediate hosts are *Crustacea*. The larval stages of the Guinea-worm, *Dracunculus mediensis*, develop in *Cyclops coronatus*, and the early larval development of *Diphyllobothrium latum* and *D. mansoni* has recently been shown to occur also in copepods, that of the former in *Cyclops strenuus* and *Diaptomus gracilis*, that of the latter in *Cyclops leukarti*. Various species of crabs and crawfishes serve as secondary intermediate hosts of certain flukes, *i. e.*, the later larval stages of the lung fluke (*Paragonimus westermanii*) develop in *Potamon obusipes*, *Potamon dehaani*, and other fresh-water crabs, and in *Astacus japonicus*. The mollusks which are intermediate hosts for various species of flukes have already been discussed.

In the dissemination of pathogenic bacteria, protozoa, and higher parasites, the common house fly, *Musca domestica*, is, without question, an important agent because it feeds upon human food, excrement, and other discharges from the human body. It undoubtedly plays a noteworthy part in spreading typhoid fever, cholera, bacillary dysentery, and possibly leprosy and other bacterial diseases. Stiles has demonstrated the presence of *Giardia* (*Lamblia*) cysts on flies which had fed on material containing this flagellate; and Wenyon and O'Connor have obtained evidence that cysts of *Endameba histolytica* may be disseminated by the house fly, although they have not succeeded in thus transmitting dysentery to kittens. They found that such cysts were in some instances passed within fifteen minutes after ingestion by the fly, but that under other conditions they were retained in the alimentary tract for as long as forty-eight hours. The resistant forms of other intestinal protozoa as well as the ova of the larger intestinal parasites, such as *Tænia solium*, *Ascaris lumbricoides*, and *Oxyuris vermicularis*, have also been shown to be carried about by flies. It is claimed that infectious ophthalmia (trachoma) is spread by the same agents. Other species of flies of the genus *Drosophila*, which may feed upon both fecal material and human food, should also be considered possible agents in the dissemination of parasitic organisms of the alimentary tract.

Intestinal myiasis results from the development in the human alimentary tract of the larvæ of various species of dipterous insects. These are ingested as eggs which have been deposited upon food and are accidental parasites. The common "blow" flies (*Calliphora*) and blue bottle flies (*Lucilia*) deposit their eggs upon meat, especially when it is beginning to decompose, and flies of the genera *Musca* and *Anthiomyia* may also deposit their ova on food, those of the latter genus usually on vegetable material. The symptoms evoked by the development of larvæ in the intestine may simulate those of dysentery with more or less fever and malaise. This condition is by no means rare in warm climates.

Blow flies may also deposit their eggs in open wounds, in the nostrils of individuals with ozena, and occasionally in the external auditory meatus of patients with otorrhea. Cutaneous carcinomata not infrequently

become infested with maggots even in temperate climates. The *screw worm*, the larva of a species of blue bottle fly (*Chrysomyia macellaria*) which may develop in the nasal cavity and occasionally in the external auditory canal, causes great pain and discomfort. Its migration to the frontal sinus may set up lesions which result in meningitis and death. As many as 350 larvæ have been removed from one patient. In some instances the soft palate and tissues about the nose are destroyed. Sneezing, swelling of the face, and discharge of a blood-stained, serous substance from the nose are fairly constant symptoms. Erysipelas may complicate the condition. Instillation of 10 per cent. chloroform in milk, or of oils, kills the larvæ in the external auditory canal.

Of the dipterous larvæ, which may cause *cutaneous myiasis* in man, certain species are normally parasitic in lower animals, and others live satisfactorily upon both the human being and lower animals. The ox "warble" (*Hypoderma bovis*) or closely related species (*Hypoderma lineata*) occur occasionally in man. The eggs which are deposited by the adult fly on the hair of its normal host are, when hatched, licked off by the animal and swallowed. The larvæ migrate to the submucous tissue of the pharynx where they remain for several months, and then through various portions of the body, including the spinal canal, finally becoming localized beneath the skin. This is penetrated to provide for the free respiration apparently necessary at this stage of development. After completing its development the larva escapes from the boil-like lesion it has produced and, entering the soil, passes into the pupal stage. Some observers state that the larvæ may enter the skin directly when they hatch from the egg. Another estrid larva of the species *Dermatobia cyaniventris* is commonly found in human beings in Brazil and other parts of South America, where it is known as "Ver Macaque." The eggs of this species are cemented by the adult fly to the body of mosquitoes, biting flies, and even ticks which feed upon cattle, horses, or other animals, so that the larvæ, on emerging while the mosquito is feeding, may penetrate the skin of the host. This mode of transference of the parasite appears to have been seen by competent observers and has long been recognized by natives who call the larva the "Guzano de Zancudo" or the "mosquito worm." Migration of the larva may cause considerable pain. After the parasite comes to rest beneath the skin a lesion forms which may attain the size of a pigeon's egg.

The human being also serves as a satisfactory host for the African skin maggot, or "Ver du Cayor," which is the larva of the "tumbu" fly (*Cordylobia anthropophaga*), a species very prevalent in Natal. The eggs are deposited upon the clothing or skin, the fly being attracted by body odors and filth. The larvæ hatch promptly, in some instances within the body of the parent fly, and penetrate the skin without causing any appreciable pain. Subcutaneous growth of the maggots may, however, produce considerable discomfort and result in the formation of boil-like lesions. After attaining full size (about $\frac{1}{2}$ inch) the maggots perforate the skin, enter the ground, and pass into the pupal stage. Infants are especially liable to be attacked by the larvæ of this species of fly.

Temporary Parasites (Blood-sucking Insects, Mites, and Ticks) which Transmit Disease.—Various species of biting flies produce painful or annoying conditions of the skin. Comparatively few species, however, are known to transmit disease. Certain Tsetse flies serve as hosts for trypano-

somes which are pathogenic to man and animals. *Glossina palpalis* transmits *Trypanosoma gambiense*, which causes the gambian form of sleeping sickness; and *Glossina morsitans* transmits *Trypanosoma rhodesiense*, which causes the rhodesian form of sleeping sickness, and also *Trypanosoma brucei*, which causes nagana, a fatal disease of cattle. Because of the active feeding habits of the tsetse fly, trypanosomes may be mechanically transferred from host to host. They do, however, undergo definite phases of development within the fly where they live for a long time, probably until the death of the insect, which thus serves as an intermediate host. Other trypanosome diseases (surra, which affects domestic animals in parts of Asia) are transmitted by biting flies of the genera *Stomoxys* and *Tabanus*. The development of the flagellate within these flies is less well known.

The spread of anterior poliomyelitis by the stable fly (*Stomoxys calcitrans*) has not been satisfactorily demonstrated. That this fly may, however, transmit anthrax as well as malignant pustule in animals, and that it serves as the intermediate host of certain parasitic worms of domestic animals, has been definitely proved.

A species of sandfly (*Phlebotomus papatasii*) transmits an acute disease known as "three-day" or "phlebotomus" fever. The causal agent of this disease is unknown, but about ten days is necessary for its development in the sandfly before the latter becomes infectious. Experimental evidence tends to indicate that cutaneous leishmaniasis is transmitted by species of Phlebotomus at least in certain regions.

The larvæ of one species of fly (*Aucheromyia luteola*) act as temporary parasites to man. These are the Congo floor maggots which feed at night upon blood obtained by puncturing the human skin.

Mosquitoes of various species transmit a number of very important pathogenic micro-organisms and parasites for which they are either definitive or intermediate hosts. Only those of the subfamily *Anophelina* serve as hosts for the parasites of malaria which have been found to develop in many species of this group. Some of these, either on account of their rarity or biological peculiarities, are of minor importance. It is found that the malaria mosquito in one region may be of a species quite distinct from that of another region or country. In the United States *Anopheles quadrimaculatus* carries nearly all the malaria, *Anopheles punctipennis* and *Anopheles crucians* being here of slight importance because they feed for the most part on lower animals and only infrequently enter human habitations. The development of the malaria parasite takes place in the adult mosquito. After sporogony in the gut wall of the mosquito the infectious forms of the parasite, the sporozoites, migrate to the salivary glands and the proboscis, whence they escape into the tissue during the act of biting. The time required for completion of this development varies with temperature, but under favorable conditions is about ten days. During this interval of development a mosquito which has ingested malarial blood cannot transmit the disease. The mosquito thus serves as the definitive host for malaria parasites.

Filaria bancrofti is also transmitted by the mosquito. The development of its larval stages in the latter has already been discussed. The mosquito in this instance serves as intermediate host since it harbors only the larval forms of the parasite. *Filaria bancrofti* is known to develop in many species of both anopheline and culicine mosquitoes.

Yellow fever is transmitted by *Aëdes calopus* (*Stegomyia fasciata*), a culicine mosquito, in which a period of development of about twelve days is necessary to render the mosquito infectious. For the mosquito to become infected it is apparently necessary for it to draw blood during the first few days of the fever.

The mosquito has also been considered a possible agent in the transmission of leishmaniasis, but no more than a slight development of the flagellate has been observed in this host.

Of the bugs that habitually attack the human being the bedbug is most generally distributed. The Indian species (*Cimex hemipterus* (*rotundatus*)) has been suspected by Patton to be a host for *Leishmania donovani*, the parasite of kala-azar. That it does transmit this disease has not, however, been demonstrated, and there is considerable evidence to the contrary. The organism which causes Indian relapsing fever has been found to live for from four to seven days in this bug after it has fed on the blood of infected monkeys. The common bedbug (*Cimex lectularius*) is supposed to transmit European relapsing fever, although the louse appears to be the normal vector. It is quite possible that the bedbug may mechanically transfer pathogenic micro-organisms, such as those of leprosy, syphilis, etc., and may maintain *Bacillus pestis* for many weeks after acquiring it.

Reduviid bugs of the genus *Triatoma* (*Conorhinus*) not only inflict painful wounds, but *Triatoma megista* and several other species transmit a form of trypanosomiasis in Brazil. A number of species of this genus have been found to harbor trypanosomes some of which may be derived from rodents and other wild animals. It is not yet known how many of these bugs can transmit trypanosomes to the human being.

Certain "harvest" mites (Trombidiidæ), while only temporarily parasitic upon the human skin, produce extremely annoying irritations and eruptions. The skin is usually attacked by the larval (six-legged) forms of such mites which because of their small size may overrun the skin before their presence is realized. The larva of a Japanese mite (*Trombidium akamushi*) is known to transmit a very fatal typhus-like disease known as "kedani" or flood fever. This species feeds in great numbers on the local field mouse (*Micromys montebelloi*). Inclusions known as "Akamushi bodies" have been described in the tissues of both infected animals and the larval mites as the etiological agent in the disease. The virus is reported to be non-filtrable.

The ticks (*Ixodidæ*) are responsible for a disease known as "tick paralysis." This occurs most frequently in sheep, but also in children. Bites over the vertebral column, especially near the head, are most prone to be followed by paralysis. This disease is associated with the bites of various species of ticks, and occurs in Oregon, British Columbia, Australia, and South Africa. There is usually an incubation period of six or seven days before the paralysis appears, first in the legs, later in the arms, thorax, and neck. There is little or no fever and in non-fatal cases recovery is rapid. The prompt removal of ticks appears to have a favorable influence on the course of the disease. It is not definitely known whether tick paralysis is infectious or whether it is caused by toxic substances derived from the ticks. From the bites of certain species of ticks serious ulcerations may arise. Rocky Mountain fever, a typhus-like disease having a high mortality,

is transmitted by *Dermacentor venustis*. A form of *Rickettsia* found in great numbers in the lesions in the wall of blood-vessels and also in infected ticks is considered by Wolbach to be the etiological agent.

African "tick fever" or relapsing fever is transmitted by the tick *Ornithodorus moubata*, in which *Spirochæta duttoni* persists through successive generations.

Adapted Parasites (Ectoparasites) which Transmit Disease.—The "itch mite" (*Sarcoptes scabiei*) develops only on the skin of its host. Those of various animals are regarded as varieties of a single species. When transferred from animals to man, certain of these may cause more or less itching and irritation, but since they cannot breed except on their normal host they soon disappear. The male dies after copulation, but the impregnated female burrows into the epidermis and produces characteristic lesions, distributed chiefly between the fingers and toes, in the groins, axillæ, and on the external genitalia. These become more generalized in severe cases. The burrows are slightly colored by the eggs and excrement deposited by the female, and measure from a few millimeters to several centimeters in length. From fifteen to fifty eggs are deposited by each female, and a new generation is produced within about four weeks. This parasite is disseminated chiefly by contact or by any means which transfers the larvæ—adults or eggs. The latter are probably only rarely transmitted from host to host. Scabies assumed great importance during the recent World War and has been placed at the head of a group of diseases which caused about 90 per cent. of all sickness in one of the British armies. Sulphur ointment is commonly employed in the treatment of scabies. By employing the twenty-four-hour Danish method in scabies, it is possible to cure the condition by a single treatment. For details of the preparation of the ointment employed and the method of its application, it is best to consult special papers on the subject (Lomholt, 1920; Greenwood, 1924).

Linguatulidæ, or "tongue worms," so named from their characteristic shape, are related to the mites, but because of their adaptation to parasitism have lost nearly all resemblance to this group. The body is composed of a large number of segments, and on the head there are two pairs of claw-like hooks at the sides of the oral aperture. The adults live in the nasal cavity, chiefly of the dog and other carnivorous animals, and the eggs when deposited are discharged in sneezing. These develop when ingested by herbivorous animals and the larvæ enter the liver and other organs. As maturity approaches, the larvæ migrate through the tissues to the mucous surfaces, whence they leave their intermediate host in discharges from the respiratory tract or alimentary canal. This, however, does not appear to be an essential step in their transference, since they may be ingested in great numbers with the flesh devoured by carnivorous animals. The species most commonly found in man (*Linguatula rhinaria*) is relatively rare and is nowhere very prevalent in animals.

Lice assume great importance under conditions of war. Their presence is not only a source of annoyance to those not accustomed to them, but permits the spread of disease which may incapacitate and destroy great populations. Lice are wingless insects adapted to life on the surface of the body and feed upon the blood of their host. There are two types which live on man—the true louse (*Pediculus*) and the pubic or "crab" louse (*Phthirius pubis*). Two species of pediculi were formerly recognized, but since they

interbreed freely, they are now both thought to belong to one species, the *Pediculus humanus*, of which the body louse (*P. humanus vestimenti*) and head louse (*P. humanus capitis*) are varieties. The latter lives upon the scalp and attaches its eggs ("nits") to the hair; the former lives in the clothing and deposits its eggs there.

As the result of the irritation arising from louse bites, pustules and crusts may be formed in the scalp and the cervical lymph-nodes may become enlarged. Eczematous lesions may also develop and spread over the face and other parts of the body. Blepharitis and conjunctivitis are frequently associated with the head louse. As the result of the bites of body lice, more or less scratching is indulged in, which produces rather characteristically distributed excoriations and lesions. When neglected, the condition may become serious, in fact, many distinguished individuals are said to have died in past times of louse disease.

Pediculus humanus transmits typhus fever, relapsing fever (North African and European), and trench fever. The louse does not become infectious until eight or ten days after biting a typhus patient; after that interval the excrement or the crushed louse scratched into the skin produces infection. This is also true in the transmission of relapsing fever. The virus of this disease may be transmitted through several generations of lice. An individual may be infected with trench fever by the bite of infected lice (the usual manner of infection) or by inoculation of the skin with louse excrement in the process of scratching. The virus of trench fever is said to be filtrable.

Fleas (*Siphonaptera*) are wingless insects more or less related to and sometimes classified with the *Diptera*, or two winged flies. Their flat bodies enable them to pass through the fur of animals which they infest, and the marked development of the posterior pair of limbs enables them to make phenomenal leaps. The eggs are large and are deposited in the fur of the animal upon which they live, or in the shed fur and rubbish of animal haunts. The eggs of the human flea, for example, are distributed in dust and débris in the cracks of floors, etc. The larvæ, which are maggot-like, feed upon bits of organic material, especially the dried blood on the shed fur of infested animals; after a period of growth they spin a cocoon and enter the pupal stage. Being voracious feeders, the adults of some species die very quickly when removed from their hosts, but others live for long periods at low temperatures, especially when protected by dust and rubbish. Although the various species of fleas are each associated with a definite host, many feed to a large extent, as the occasion affords, on animals other than their normal host. During feeding, considerable quantities of blood may pass undigested through the alimentary tract, and when such dejecta dries upon hair or fur it serves as food for larval fleas.

The rat flea (*Xenopsylla cheopis*) is probably the most important agent in the transmission of bubonic plague. *Bacillus pestis* multiplies rapidly in the alimentary tract of this species, and it is said that infected fleas are abnormally active, moving from place to place rather than gorging themselves at one spot. It is quite generally conceded that infection of man is usually accomplished by inoculation of the skin with the excrement of the flea during scratching or rubbing. It is notable that cleanly habits, especially the daily bath, greatly diminish the chance of infection even though there may be exposure to infected fleas. It is said, however, that the

growth of bacilli in infected fleas produces more or less obstruction of the alimentary tract so that infectious material may be regurgitated into the bite wound. Other species that attack both man and susceptible animals may transmit the disease. Thus the human flea, *Pulex irritans*, the European rat flea, *Ceratophyllus fasciatus*, and the Californian squirrel fleas (*Hoplopsyllus anomalus* and *Ceratophyllus acutus*) are known to carry the infection.

Various measures are employed in destroying fleas, such as the destruction of animals which serve as hosts, strict adherence to habits of cleanliness, the filling of cracks, the use of naphthalene, or fumigation. Powdered sodium fluorid is a very effective destructive agent. Water is particularly useful in the prevention of the breeding of fleas, and, by the daily use of the hose, kennels and animal quarters may be kept comparatively free of these pests.

The "chigger," "jigger," or sand flea (*Dermatophilus penetrans*) attacks a variety of hosts, especially the human being and the pig. The impregnated female burrows into the skin, usually about the toes, and then becomes so greatly distended with eggs as to acquire the size of a small pea. The two posterior segments of the body plug the opening in the skin so that the eggs are discharged on the surface. The larvæ develop in dry sandy soil. Proper footwear and leggings to a large extent prevent the attacks of this flea.

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DISEASES OF ALLERGY

SERUM DISEASE AND SERUM ACCIDENTS

Definition.—Serum disease is an allergic reaction resulting from the parenteral administration of a foreign serum and characterized by an incubation period, skin eruptions, enlargement of lymph-nodes, fever, edema, and polyarthritis. It should be distinguished from the immediate shock-like, and sometimes fatal reactions, which occur when foreign serum is administered parenterally to an individual who is hypersensitive to the serum employed. These latter reactions are better called serum accidents. Since individuals manifest all degrees of hypersensitiveness from complete insensitiveness to a condition of extreme sensitization, transition forms between mild serum disease and severe serum accidents may occur.

History.—Although animal blood had occasionally been used in transfusions since the seventeenth century and various untoward effects noted, not until 1875 (Landois and Ponfick) was there any appreciation of the important difference between human and animal blood for transfusions. Generalized urticaria ten days after transfusion of alien blood was reported in 1874 (Dallera), but its significance was not understood. When diphtheria antitoxin came into general use in 1890 the symptoms of serum disease and serum accidents soon attracted wide-spread attention. At first they were ascribed to the antitoxin content and then to some other unknown constituent of the horse serum, but Johannessen (1895) showed that normal horse serum was equally effective. The first systematic study of the clinical and immunological phenomena of serum disease was undertaken by von Pirquet and Schick; their results were published in a monograph in 1905. Their work defined and illuminated the problem and has stimulated many others during the past twenty years to investigate the incidence, symptomatology, and mechanism of serum reactions.

Incidence.—Not every patient treated with serum develops serum disease. If amounts below 10 c.c. are used, only about 10 per cent. have symptoms, but if 100 c.c. or more are administered, only 10 per cent. escape at least some manifestation of serum disease. The incidence, therefore, depends largely upon the amount of serum given. Race is also a factor, but of less numerical importance. Negroes and American Indians are less susceptible than the white race. Age, sex, the disease for which serum is given, and the route of administration seem to have little or no effect on incidence. For some obscure reason the serum from certain horses produces serum disease more frequently than that from others.

Pathogenesis.—Precipitins for the foreign serum are usually in the circulation after the ninth or tenth day. In severe cases they are apt to reach a high titer, and in patients who, despite large amounts of serum, have little or no serum disease, they are usually absent, transitory, or of low titer. When the precipitin in the circulation reaches a high titer the foreign serum still in the circulation disappears rapidly; when no precipitin is demonstrable the disappearance of the foreign serum from the circulation is greatly retarded. The symptoms of serum disease are thought to be due to a union of the foreign serum with the specific precipitin which has been elaborated during the incubation period, but the possibility has not been excluded that the symptoms are an expression of the immune reaction involved in the production of antibody rather than the result of a union between antigen and antibody.

Symptoms.—When large amounts of serum are administered the *severity of the symptoms* is determined chiefly by the constitutional susceptibility of the individual. A liter of serum given during the course of two or three days may produce nothing more than a few urticarial wheals and slight enlargement of the superficial lymph-nodes for a day or two. Other patients, after receiving a few cubic centimeters of serum, may have severe urticaria, edema, fever, arthritis, and swollen tender lymph-nodes for one or two weeks. Exceptionally, the symptoms persist for three weeks or longer. In a large proportion of patients they subside after four to six days. When such amounts of serum as are commonly employed in diphtheria and tetanus immunization have been administered, the severity as well as the incidence of symptoms tends to be less than after the large amounts given for pneumonia (Type I) and meningococcus meningitis. But even after small quantities of serum given subcutaneously, an occasional patient may have severe and prolonged serum disease. The nature of the constitutional factor which determines to a large extent the incidence and severity of serum disease is quite unknown.

Serum disease without *skin manifestations* is very rare. The eruption is usually urticarial or a mixture of urticaria and erythema. Itching of the skin often comes first; then patches of erythema and discrete wheals appear; the wheals with a circumferential halo of erythema may remain discrete, or as the eruption becomes more intense large wheals, the size of the palm of the hand, appear, and by confluence form bizarre patterns over the chest, back, or extremities. The face is usually affected. Itching is often intense. Occasionally the eruption is morbilliform or scarletiniform, but these atypical varieties are more often seen during a relapse than during the initial sickness. Purpuric rashes are occasionally observed in serum disease of more than average severity. The eruption usually disappears after three to five days. When the serum has been administered subcutaneously or intramuscularly, the earliest eruption is apt to be at the site of the injection. It may remain confined to this area—the so-called local serum disease—or subsequently become generalized.

Slight or moderate enlargement of the *superficial lymph-nodes* is usually present. Often this is the first symptom, antedating the eruption by one or two days. The nodes may or may not be tender. Frequently the epitrochlears are the first nodes in which the enlargement can be felt. After the other symptoms of serum disease have subsided the nodes often remain enlarged for several days. When the serum has been administered under the skin or into the muscles the regional nodes are apt to be the first to increase in size. Slight enlargement of the spleen is not infrequent.

After large amounts of serum, 50 to 60 per cent. of patients with serum disease show some evidence of *arthritis*. In most cases objective changes are slight or absent. The patient complains of pain and stiffness, but there is little to be seen or felt. In a small proportion of cases the joints are swollen, hot, red, and distended with an exudate which has an interesting similarity to the joint fluid of rheumatic fever (Swift and Boots). It is turbid and contains leukocytes up to or above 20,000 per cubic millimeter. Polymorphonuclear cells usually predominate. A precipitin test often reveals the presence of horse-serum in the joint exudate. The commonly involved joints are the knees, ankles, elbows, wrists, and small joints of hands and feet. Less commonly the other joints are affected. The tem-

poromaxillary joints are involved more often in serum disease than in rheumatic fever. It is unusual for joint symptoms to appear at the onset of serum disease.

Fever occurs in about one-third of the cases. From an elevation of only 1 degree for a day or two, all gradations are observed. In severe cases the temperature may reach 103° or 104° F. every day for a week or ten days. It is usually an irregular and remittent type of temperature curve.

Edema occurs also in about one-third of the cases. The face, sacral and pretibial regions, ankles, hands, and arms are the areas where it is most often noted. Chlorid and water retention, a lowered phthalein excretion, moderate oliguria, albuminuria, and cylindruria are not unusual concomitants of the edema. Rarely, if ever, is there a measurable *nitrogen retention*. After the serum disease has subsided, all evidence of impaired renal function vanishes. Attempts to demonstrate horse serum in the urine have been unsuccessful. *Optic neuritis*, with a slight increase of the cells and globulin in the spinal fluid, may be observed occasionally.

In adults there is frequently no change in the *blood picture*. von Pirquet and Schick found that children show a leukocytosis during the incubation period, and leukopenia after symptoms develop. Such changes rarely occur in adults. Even severe cases may show nothing abnormal in the blood-count or there may be a mild leukocytosis while symptoms are present, and toward the end or after the period of symptoms an increase of the eosinophil cells.

Other symptoms occasionally observed without any other explanation than that they are a part of the serum disease are: abdominal pain, vomiting, diarrhea, stupor, headache, conjunctivitis, and sore throat.

Relapses occur, in our experience, after a free interval of from four to fourteen days. With a recurrence of symptoms the eruption is more apt to be erythematous, morbilliform or multiform than urticarial. Any of the other symptoms may be present. There are two observations supporting the belief that relapses represent reactions to antigenic constituents of the foreign serum different from those responsible for the initial outbreak of symptoms. Dale and Hartley showed that when an animal is sensitized to a foreign serum, sensitization to the serum albumin develops later than to the serum globulin, and Coca found no relapses in 129 patients with serum disease due to a diphtheria antitoxin consisting of the isolated pseudoglobulin.

Diagnosis.—Very rarely is there any difficulty in recognizing serum disease. Occasionally a relapse with an atypical or inconspicuous eruption may cause uncertainty. It is sometimes difficult to decide whether fever, occurring during or immediately after a serum eruption, is due to a complication of the disease for which the serum was given or to the serum disease. A leukocyte count below 12,000 or an eosinophilia is in such cases evidence in favor of serum disease.

Prognosis.—Fatalities from serum disease itself are unknown. Complete recovery, even from the severe forms, is almost invariable, provided the infectious disease for which the serum was administered leaves no permanent ill-effects. A high percentage of individuals retain for years some degree of sensitization to the serum employed; yet with proper precautions the same kind of serum can be administered subsequently to nearly all of these patients.

Treatment.—It has not been demonstrated that serum disease can be prevented. A certain amount of symptomatic relief is the most that can be expected. For the pruritis, calamine lotion containing 1 per cent. phenol is often helpful. Bicarbonate of soda baths may give temporary relief even in severe cases. Salicylates are ineffective in the treatment of the arthritis, but seem to mitigate the joint symptoms if given in large doses soon after the administration of the serum.

SERUM ACCIDENTS

Definition.—Serum accidents are the immediate, shock-like, sometimes fatal, reactions which occur in individuals who are hypersensitive to the serum administered.

Etiology.—The essential cause of these reactions resides in the specific reactivity of the individual. Persons susceptible to asthma or to rhinitis and coryza when in proximity of horses are most likely to have serious serum accidents. Those sensitized by a previous injection of serum may also have alarming or, rarely, even fatal reactions, but in general are less sensitive than the "horse asthmatic" group. Certain individuals also who have never experienced symptoms from contact with horses and who have not received a previous injection of serum, show a positive skin reaction to horse serum and hence must be considered hypersensitive.

Pathogenesis.—Despite certain dissenting opinions, most competent authorities look upon serum accidents as examples of anaphylaxis. The fact that the majority have occurred in spontaneously hypersensitive individuals upon the first injection of serum has been urged as a reason for separating this group of serum reactions from anaphylaxis. In those cases in which the first serum injection is tolerated without immediate symptoms and a subsequent serum injection after weeks or months has unloosed immediate and violent symptoms, the analogy with experimental anaphylaxis is nearly complete. The chief discrepancy is found in the phenomena of desensitization.

Symptoms.—The *onset* of symptoms may be lightning-like. Almost before the needle is withdrawn local itching and edema develop. A feeling of apprehension, generalized urticaria, often sneezing and a prickling sensation of the throat, edema of face, hands, neck, or perhaps of the whole body, cyanosis, choking sensation, cough, and violent asthma are common symptoms. The pupils dilate, the pulse becomes thready or imperceptible; the temperature rises; convulsions may occur, and the patient may be dead in less than ten minutes; in other fatal cases several hours may elapse between injection and death. If the serum accident does not terminate fatally, the symptoms may become those of serum disease at once or after a free interval of several days.

Treatment.—The *prophylaxis* of serum accidents consists of (1) recognition of those who are hypersensitive before administering serum; (2) desensitization of hypersensitive individuals.

A history of asthma or hay-fever should make one cautious in giving serum, particularly if the patient has experienced such symptoms when near horses or stables. A history of previous serum administration also calls for precautionary measures. An intracutaneous test with a 1 : 10 solution of horse serum should be made. If this is positive, the patient should be considered an unsafe subject for serum therapy by routine methods.

Desensitization offers a method of administering serum safely to many patients who would otherwise react violently or even fatally if the whole amount of serum were injected in the usual way. The genuine "horse asthmatic" may in some instances be so highly sensitive that he cannot be desensitized, but most of those whose hypersensitiveness dates from a previous serum treatment can, in the course of twelve to twenty-four hours, be rendered sufficiently tolerant to take therapeutic quantities without danger. If there is a history of asthma or a strongly positive skin test, the first desensitizing dose should be given *subcutaneously*. Beginning with 0.005 to 0.025 c.c. according to the intensity of the skin reaction, the dose may be doubled every half-hour until 1 c.c. is given. Then 0.1 c.c. is injected intravenously. Dilution with normal salt solution is advisable because thereby injection may be made more slowly. The *intravenous* dose should be doubled every twenty to thirty minutes until the required amount has been given. In case anything more than a mild reaction occurs one should wait the usual interval or longer, and then repeat the last dose which produced only a mild reaction or none at all. If the serum is to be administered *intraspinally*, the same procedure should be carried out until five or six of the intravenous doses have been given. Then with diluted serum the intraspinal route may be tried slowly and cautiously. With patients only slightly sensitive, as often proves to be the case when hypersensitiveness has been artificially produced by a previous serum treatment, the desensitization program outlined may be shortened by starting with a slightly larger dose and increasing the size of the doses a little faster.

One should always have on hand, when attempting desensitization, a syringe containing *epinephrin* ready for use. Epinephrin is a specific for serum accidents. Subcutaneous injection of 0.3 to 0.8 c.c. (5–12 minims) will usually prove effective in the milder accidents. Injection should be repeated after a few minutes if necessary. If the symptoms are alarming, larger doses are indicated. *Atropin*, gr. 1/60 to gr. 1/30 (0.001–0.002 gm.), subcutaneously, is also recommended.

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HAY-FEVER

(*Atopic or Allergic Coryza*)

The condition generally known as hay-fever, but more properly termed "atopic" or "allergic coryza," is a manifestation of the so-called hypersensitive reaction. The term *hypersensitiveness* is now used medically in a

restricted sense to indicate a certain group of biological reactions that occur in man and that are mediated by a special mechanism. They are not to be considered as toxic reactions, for the specific substance known as atopen or allergen, to which the reaction occurs, is not toxic for the normal individual. The reactivity depends upon a substance within the cells and in the serum of the hypersensitive man. In this chapter we are concerned solely with the reactions of the upper respiratory tract whose clinical manifestations are those of an irritative coryza with ocular manifestations. By far the greater number of cases of atopic (allergic) coryza are caused by pollens and, therefore, more particular attention will be paid to this group, designated as *seasonal hay-fever*, because the clinical symptoms occur with seasonal regularity. It must be borne in mind that the seasonal periodicity of these attacks is not due to any seasonal change in the specific reactivity of the individual. The clinical symptoms are intermittent merely because the contact with the pollen is intermittent. A second and by no means small group of cases has identical symptoms either continuously or intermittently throughout the year, and is called *perennial or non-seasonal hay-fever*. It corresponds with the group to which the term "vasomotor rhinitis" is applied. The perennial nature of the attack is due to the fact that the excitant or specific substance may be present at any and all times of the year. The mechanism of the reaction is the same in both groups.

SEASONAL TYPE OF HAY-FEVER

(*Rose Cold, Pollinosis*)

History.—The following facts stand out as important in the development of our present conception of the nature, the causative factors, and the treatment of hay-fever. Bostock in 1819 identified the seasonal coryza as a clinical entity. Elliotson in 1831 suggested the pollens as causative factors. In 1873 Blakeley, a hay-fever victim, used extracts of pollens upon himself and was able to precipitate an attack. Dunbar, conceiving that the pollen contained a toxic albumin, attempted to immunize horses against it. He believed that the serum of injected horses contained a specific antitoxin, and this immune horse serum was used in the treatment of hay-fever and sold under the trade name of "Pollantin." More recently it has been shown that this serum from supposedly immune horses does not contain any specific pollen antibody. Wolff Eisner in 1906 suggested that hay-fever was a specific anaphylactic reaction. Freeman and Noon in 1911 were the first to publish their results on the treatment of hay-fever by active immunization with pollen extracts. Clowes in 1913 reported on the specific reactions exhibited by hay-fever cases. Cooke in 1915 reported on 144 cases treated by injection with extracts of pollen. Since this time a very considerable amount of work has been done; the important pollens have been determined, and the technic of diagnosis and the method of treatment have been fairly well systematized.

Etiology.—In general, the air-borne pollens are the important etiological factors, but almost any pollen may be a factor when it is presented in sufficient concentration to the specifically sensitive individual. In the eastern part of the United States it is possible to distinguish three seasonal varieties of hay-fever. First, the *spring type* begins at the end of March or early April and extends to the end of May. This is due almost entirely to the pollens of trees, especially of the oak, elm, maple, birch, and hickory. The second type, beginning at the end of May and extending to the middle of July, is caused almost entirely by the pollens of grasses and is designated as the *summer type*. The important pollens in this group are timothy, redtop, June grass, orchard grass, sweet vernal, and plantain. The third or *fall type* begins in the middle of August and continues until frost. The pollens of the ragweeds are mainly responsible for this group.

Incidence.—Heredity is the only known factor in the pathogenesis of hay-fever.

Morbid Physiology.—In 1919 Ramirez reported what appeared to be a passive transfer of hypersensitiveness by means of blood transfusion. The donor was hypersensitive to horse dander and had clinical symptoms of coryza and asthma on exposure to horses. Following transfusion the recipient developed an attack of asthma after exposure to a horse. He had never had asthma prior to the transfusion. In 1921 Prausnitz demonstrated the fact that the serum of a fish-sensitive patient when injected intradermally into a normal man produced a localized skin sensitiveness to the same fish preparation, whereas the other areas of skin in the normal man showed no evidence of sensitiveness whatsoever. deBesche confirmed this observation of the passive transfer of sensitiveness, and more recently Coca and Grove have confirmed and extended these observations which establish the fact that the blood-serum of clinically sensitive cases contains a substance which reacts specifically with the atopen (allergen) to which the donor is sensitive.

The earliest observations on cases of human hypersensitiveness had long shown that the hypersensitive reaction can be demonstrated in the skin as well as in the mucous membranes of individuals with clinical hay-fever and asthma. This general skin sensitiveness is made use of in diagnosis.

Morbid Anatomy.—There is no organic pathology in uncomplicated seasonal coryza. The bony and cartilaginous structure and the mucous membrane of the nose may be as normal in appearance in patients with hay-fever during the free period as they are in the normal man. The only organic lesions which may be present are polypoid degeneration and secondary infection of the paranasal sinuses.

Symptoms.—The symptoms of hay-fever are essentially local, being due to the atopic reaction occurring in the mucous membranes of the eye, nose, and pharynx. These symptoms vary considerably in their severity according to the degree of sensitiveness of the particular individual. In occasional cases peculiar variations have been noted, such as those in which the symptoms are entirely nasal and there is no clinical ophthalmic reaction. Or, more rarely, one eye only is involved or one eye is much more sensitive than the other. During the attack the symptoms vary greatly in severity from day to day or even from hour to hour. They consist of an *itching* and *congestion*, sometimes even of an edema, of the mucous membrane of the sclera and conjunctiva. *Photophobia* of greater or less degree results. There is itching of the nose, sometimes even of the skin over the nose and of the face. *Sneezing* occurs in paroxysms, is violent, and is accompanied by a thin, alkaline, irritating, serous discharge. Congestion and edema of the mucous membrane of the nose occurs, and when the edema is great there may be complete obstruction to nasal breathing. Itching is often felt in the ears, on the roof of the mouth, and in the pharynx.

The clinical picture of seasonal hay-fever is quite typical. It is particularly characterized by its strict seasonal occurrence and by the fact that in any given individual the attack from year to year begins and ends on approximately the same date. This is quite readily explained by the fact that in any given locality the pollination of any particular plant is very little influenced by weather variations.

One important point with regard to all cases of hypersensitiveness must

be borne in mind, namely, that over 50 per cent. of the patients are hypersensitive to more than one atopen. As a matter of fact, approximately 33 per cent. of the patients with the summer type of hay-fever are sensitive also to the pollen of ragweed, so that it is not uncommon for seasonal hay-fever to begin in the spring and continue throughout the summer. The essential point is that attacks do not occur during the winter months. On the other hand, a form of seasonal hay-fever is not infrequently combined with the perennial types of coryza to be described later. There may be a perennial disturbance, with exacerbations occurring in the spring or summer or fall. These complex manifestations can only be recognized by means of the diagnostic tests. Occasionally typical seasonal hay-fever, the fall type for example, does not cease at the time of frost, but continues into the winter. This may be the result of an additional atopic reaction, or of secondary sinus infection.

Complications.—*Multiple atopic reactions* are to be considered as complications of typical hay-fever. They can only be differentiated by careful diagnostic skin tests.

Infection.—Infections of the paranasal sinuses occur in a large percentage of cases, but in only a relatively small percentage does this infection become clinically important and warrant special treatment.

Asthma.—There is one type of asthma which is strictly atopic and caused by the hypersensitive reaction in the bronchial mucous membrane. Here the attack is as typically seasonal as hay-fever. Usually in these cases the asthmatic manifestations do not begin until the symptoms of hay-fever have been present for about two weeks. Asthma of this type occurs in about 15 per cent. of all cases of hay-fever. There is also a type of asthma which results from infection of the paranasal sinuses. This form usually develops late in the course of the attack of hay-fever and may persist long after the seasonal limits for hay-fever.

Pollen Preparations.—Of the many methods of preparing and standardizing the pollen extracts, the most satisfactory is that in which the extract used for therapeutic injections is identical with that used for the cutaneous and ophthalmic test. Extracts containing glycerin and alcohol cannot be used in this way. The best method of preparation is that published by Coca in which the extract is standardized by the nitrogen content. From the stock extract the following dilutions are made for test and treatment:

Solution	1	contains	0.00001	mgm.	of	nitrogen	per	c.c.
"	2	"	0.0001	"	"	"	"	"
"	3	"	0.001	"	"	"	"	"
"	4	"	0.01	"	"	"	"	"
"	5	"	0.1	"	"	"	"	"

Gradual deterioration of these pollen extracts is a difficulty that has not been overcome. As it is probably due to enzyme action, great care must be exercised in keeping the extracts cold during preparation and throughout the period of use. When proper attention is paid to these details the extracts are entirely satisfactory for about six months. The methods of collection of the pollens will not be discussed here since satisfactory preparations of the important ones may now be obtained from reliable sources.

Diagnosis.—The determination of the specific pollens to which an individual may be sensitive is carried out by means of cutaneous and ophthalmic tests.

1. Cutaneous Test.—The cutaneous test may be performed in two ways. In the *scarification method* the desiccated or fluid extract of pollen or the pollen itself is applied to a small scarified area of the skin. In the *intradermal method* the extract of pollen is introduced into the most superficial layer of the skin through a fine hypodermic needle (26 gauge). The

amount injected in any one test is about 1/50 to 1/100 c.c. This forms a small papule from 2 to 3 mm. in diameter. Using either method, from six to eight tests may be made at any one time. The intradermal method is the more delicate and accurate of the two, but for anyone not experienced in the use of the tests the scarification method is perhaps the safer.

Tests are negative when there is no increase in the size of the original papule, no zone of hyperemia, and no itching. *Positive reactions* are designated as "marked," "moderate," or "slight." In the *marked reaction* from five to fifteen minutes after the introduction of the extract there is the development of an urticarial wheal with irregular outline and pseudopod projections extending out into a zone of hyperemia. This wheal may vary from $\frac{1}{4}$ inch to several inches in diameter if the reaction is very marked. When the wheal exceeds an inch in diameter the subject is exquisitely sensitive to the extract in the concentration in which it was used, and a general or constitutional reaction may result. Itching practically always accompanies these reactions. The wheal usually fades within two to four hours and becomes blended with the surrounding zone of hyperemia, which may last from six to twenty-four hours. Occasionally, even at the end of thirty-six hours, there is still hyperemia and edema at the site of the test. *Moderately positive reactions* are merely less severe than the marked reactions. There is a decided increase in the size of the papule without the marginal irregularity or pseudopod formation characteristic of the marked reaction. There is usually a zone of hyperemia, and itching. Such reactions usually fade entirely within two to four hours. A *slight reaction* is indicated by very little increase in the size of the original papule. There is a small zone of hyperemia, and itching may or may not be present. Such manifestations fade in one to two hours.

Absolute reliance cannot be placed upon the positive skin test in the diagnosis of a clinical hay-fever. A marked positive reaction that can be verified at will is pathognomonic only of a cutaneous hypersensitiveness. The ophthalmic reaction to be described later is used for the determination of the hypersensitiveness of the mucous membrane.

Titration of Sensitivity.—As there is a very striking variation in the reaction of different individuals, it has been necessary to estimate quantitatively the degree of sensitiveness. This consists really of a titration *in vivo* of the amount of reacting substance present in the cells and serum of the patient. This principle of titration may be carried out with the ophthalmic test, but experience has shown that the reaction of the skin is a truer indication of the degree of general sensitiveness. The patient is first tested with solutions 2 and 3. If solution 2 causes marked reaction he is then tested with solution 1. If solution 2 or 3 does not produce a marked reaction solution 4 is used. On the basis of such tests cases are classified as follows:

Reaction to solution.*	Class A.	Class B.	Class C.
No. 1.....	Moderate.	Slight.	Negative.
No. 2.....	Marked.	Moderate.	Slight.
No. 3.....	Marked plus†	Marked.	Moderate.
No. 4.....	.....	Marked plus.†	Marked.

* The strength of these solutions is given on previous page.
† "Marked plus" means that the wheals are over 2.5 c.mm. in diameter.

2. Ophthalmic Test.—In the ophthalmic test a drop of the same pollen extracts as are used in the skin test is instilled into the con-

junctival sac of the eye. When the *reaction is negative* there is no change. A *positive reaction* is indicated by itching of the eye, lacrimation, and congestion of the scleral and conjunctival mucous membrane. In some cases the pollen extract is carried into the nose through the nasal duct and causes a nasal reaction, with sneezing, itching, and serous discharge. A positive ophthalmic test is pathognomonic of clinical hypersensitiveness and for this reason is important in the determination of the specific atopen (allergen). As to the relative value of the cutaneous and ophthalmic test, the positive ophthalmic reaction may be considered a sign of mucous membrane hypersensitiveness and indicates that whenever the patient comes in contact with this atopen under natural conditions a reaction is bound to ensue. The ophthalmic test is not as delicate as the cutaneous and only a limited number can be made. Furthermore, this test cannot be employed during an attack. The cutaneous test serves better for the titration of the degree of sensitiveness and has not the technical limitations of the ophthalmic reaction.

The first important point in the diagnosis of hay-fever is to obtain an accurate history of the time of onset and offset of the attack. From this history information as to the probable specific factor is gained; but one should always bear in mind the fact that multiple sensitizations are present in about half of the cases, and it is therefore wise to test with the more important substances that are causative factors in the perennial types of hay-fever. (See *Non-seasonal Hay-fever.*) If a reaction is obtained to one of the grasses the reactions to all other pollens of grasses will be of about the same degree. If a patient reacts to one of the varieties of ragweed, a similar reaction is always obtained from the others. The same cannot be said, however, for the pollens of trees, because no uniformity of reaction has been found except with species of the same genus. For this reason all of the more important tree pollens must be tested if the patient's history indicates hypersensitiveness to this group.

Treatment.—Climatic.—There is no particular locality in which the patient suffering from the *spring* or *summer type* of hay-fever may be assured of complete relief except upon the ocean. Patients suffering with the *autumnal type* may avoid the attack in the White Mountains, on the coast of Maine, in Florida, California, and Europe.

Drug Therapy.—Cocain, of course, temporarily modifies the attack, but except in cases of the utmost severity its use is not warranted. Epinephrin in the form of nasal sprays is usually irritative and produces a secondary reaction that is worse than the original condition.

Specific Treatment.—*Prophylactic.*—The specific treatment of hay-fever by means of pollen extracts is well established. Having first determined by means of the tests the proper pollen extracts to be used, and the degree of sensitiveness of the individual to these pollens, that is, having classified a patient according to the scheme previously outlined, treatment is begun with subcutaneous injections about ten weeks in advance of the expected attack. Increasing doses are given at approximately weekly intervals, according to Table 1.

The maximum dose which is attained at or about the period of clinical onset is maintained without further increase throughout the season. With the earlier doses there is usually some reaction at the site of injection, with swelling and itching lasting for twelve to twenty-four hours. If the local

TABLE 1

PROPHYLACTIC TREATMENT

Approximate Dosage According to Degree of Sensitivity

Number of injection.	Mgm. of N.		
	Class A.	Class B.	Class C.
1	0.00001 (*a*)	0.0001 (*b*)	0.0005
2	0.00002	0.0002	0.001
3	0.00004	0.0004	0.002
4	0.00007	0.0007	0.004
5	0.0001	0.001	0.007
6	0.0002	0.002	0.01
7	0.0004	0.004	0.015
8	0.0007	0.007	0.02
9	0.001	0.01	0.03
10	0.001	0.01	0.04
11	0.001	0.01	0.06
12	0.001	0.01	0.08
13	0.001 (*c*)	0.01 (*d*)	0.1 (*e*)

Notes.—(*a*) 1/10 c.c. solution 2. (*b*) 1/10 c.c. solution 3. (*c*) 0.001 continued weekly throughout the season. (*d*) 0.01 continued weekly throughout the season. (*e*) 0.1 continued weekly throughout the season.

reaction persists longer than forty-eight hours, the subsequent dose should not be increased for fear of a general reaction.

PHYLACTIC TREATMENT.—Phylactic treatment is necessary when patients apply for treatment during or just before the onset of the attack. Here the same method of diagnosis by means of the cutaneous test is necessary. The ophthalmic test is useless after the attack has begun. The injections are continued to the end of the season according to Table 2.

TABLE 2

PHYLACTIC TREATMENT

Approximate Dosage According to Degree of Sensitivity

Time.	Mgm. of N.		
	Class A.	Class B.	Class C.
1st day	0.00001	0.0001	0.0005
2d day	0.00001	0.0001	0.0005
3d day	0.00001	0.0001	0.0005
After 2 days	0.00002	0.0002	0.001
" 2 "	0.00003	0.0003	0.002
" 3 "	0.00004	0.0004	0.003
" 3 "	0.00006	0.0006	0.005
" 3 "	0.00008	0.0008	0.007
" 3 "	0.0001*	0.001*	0.01*

* This dose is continued every three to five days to end of season.

Constitutional Reactions.—These begin very quickly after the injection, sometimes within a few minutes, practically always within an hour. The sooner they begin the more severe and the more dangerous they are. The symptoms of the constitutional reaction are a general cutaneous erythema, urticaria, and itching, with marked coryzal symptoms both nasal and

ophthalmic. Occasionally there is edema of the eyelids and of the face. Asthma is the symptom that makes the reaction dangerous, and an asthmatic attack may begin even if there is no clinical history of asthma as a part of the hay-fever itself. These constitutional reactions should be immediately recognized and treated by liberal subcutaneous injection of epinephrin (1 : 1000 solution in amounts of 0.5–1.0 c.cm.). This should be repeated frequently in order to control the attack. If the attack is very severe the injection should be given intravenously. No limit should be put upon the dosage, for under these conditions enormous quantities are tolerated. *Morphin* is also indicated in the usual dose. In very severe attacks, when there is indication of dilatation of the heart caused by the intense dyspnea, *strophanthin* administered intravenously is helpful. At the onset of such an attack and when the injection has been given in an extremity, it is wise to apply a tourniquet very tightly above the site of injection in order to delay further absorption into the general circulation.

The reason for the beneficial results of the injection of pollen extracts has not yet been discovered. After a complete course of treatments the cutaneous and ophthalmic reactions are still obtained with about the same degree of intensity as before the treatment. The effects of the injections are not permanent. As a rule the course of treatment must be continued from year to year, although in general it is observed that the sensitivity tends to decrease after several years of treatment. Nothing approximating a permanent cure is assured. That the treatment is effective is demonstrated by the clinical results that have been obtained consistently over a period of ten years. In 80 to 90 per cent. of the cases treated the coryzal symptoms are almost entirely eliminated. It is very difficult to secure a complete absence of coryzal symptoms throughout the entire season. In those cases in which asthma occurs as a part of the atopic reaction the results are even more satisfactory. In over 50 per cent. of the cases with clinical asthma this symptom is entirely absent.

NON-SEASONAL TYPE OF HAY-FEVER

(Perennial Hay-fever, Vasomotor Rhinitis)

Definition.—This clinical condition differs from the seasonal type in its specific causes and in the fact that the attacks are not regularly seasonal, but may be continuous or paroxysmal throughout the year. The pathogenesis, functional pathology, symptoms, complications, diagnosis, and diagnostic technic of the seasonal type apply also to this type.

Etiology.—The most important excitants are:

1. Absorbed by inhalation:
   (*a*) Animal danders: Horse, cat, dog, rabbit, goat, cow, guinea-pig, chicken, goose, duck.
   (*b*) Vegetable powders: Orris, rice, corn, wheat, seed of cotton, kapok, flax, dust of hay and straw (not pollen).
   (*c*) House dust.
2. Absorbed by ingestion:
   (*a*) Foods: Milk, egg, fish, shellfish, nuts, chocolate, coffee, buckwheat, celery, bean.
   (*b*) Drugs: Quinin, aspirin, ipecac, senna, iodin, morphin.

When the attack is precipitated by ingestion of the atopen, the coryzal symptoms are usually but the minor part of a general reaction with urticaria, erythema, angioneurotic edema, asthma, and gastro-intestinal disturbance.

The air-borne substances absorbed by inhalation are the actual causes in nearly all instances. They are encountered most frequently in the home, but often at work, or casually. The materials from which pillows, mattresses, quilts, and upholstered furniture are made are numerous and varied: rabbit hair and goat or sheep wool are often found; the feathers of chicken, goose, and duck are, of course, commonly used. The unrefined cotton and kapok used in bedding contain particles of the seeds, and are particularly active in specifically sensitive cases. Orris root, rice powder, and cornstarch are frequent ingredients of cosmetic powders. Cereal flour acts rarely after ingestion, usually by inhalation, and is, therefore, a more common cause of the disturbance among cooks and bakers. House dust is probably the commonest specific agent. The irritant in this seems to be different from all the known substances and as yet has not been identified. The dust of hay or straw is distinct and bears no relation to their respective pollens. It is an etiological factor among farmers and those who sleep on bedding made of grass and straw.

Treatment.—The diagnostic tests are carried out by the scratch or intradermal methods used for seasonal hay-fever. It is particularly important in this type, however, to determine not only that an individual reacts to the test and that the reaction can be verified at will, but also that the individual has actually come in contact with the reacting substance and that it is truly the exciting cause. In other words, one must differentiate between *actual* and *potential* excitants.

The therapeutic principle best applied to the management of these cases is *strict avoidance of all contact with the actual excitants.* If the reaction is to feathers all chance of contact with feathers must be removed. Particular attention must be paid to cleanliness, and the home should be kept as free from dust as possible. At times, change of occupation is required. Foods, if causative agents, must be eliminated from the diet. When contact cannot be avoided, treatment by injection may be employed. The principles of treatment and the procedures are the same as those outlined above for seasonal hay-fever. The disadvantage of this form of treatment lies in the fact that since any immunization is more or less temporary it must be continued for a long time.

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ASTHMA

Definition.—Asthma is dyspnea of a characteristic "wheezy" type caused by obstruction to the flow of air in and out of the lungs usually by spasm of the bronchial muscles and edema of the bronchial mucous membrane. Such wheezy breathing occurs in a variety of conditions, and may be either continuous or paroxysmal; hence the term "*asthma*" should be used to indicate not a disease, but a symptom. "*Bronchial asthma*" is a term which is loosely applied to a syndrome exhibited by patients who between attacks of asthma are subjectively and objectively well.

History.—Asthma was first described by John Floyer who published in 1698 a "Treatise of the Asthma," in which he described his own symptoms in a remarkably accurate manner. Although as early as 1819 Bostock thought that *Catarrhus Aestivus* might come from the "effluvium of new hay," and Blackley in 1865 demonstrated that itching, swelling, and edema followed application of pollen to the forearm of patients with hay-fever, the relation between hay-fever and asthma to dusts of all kinds, including plant pollens and the odor of animals, was not seriously considered until the work of Dunbar in 1905. In 1906 Wolff-Eisner demonstrated the specificity of pollens and initiated the study of pollen chemistry. Von Pirquet's description of serum disease appeared in 1905 and was followed by many studies of the relation of foreign serum to man; these investigations, however, dealt with artificial serum disease and not with asthma.

In 1910, Meltzer recognized that the symptoms and pathology of anaphylactic shock in the guinea-pig were quite similar to those of asthma. During the next few years many different authors described the symptoms which follow contact with particular proteins in susceptible individuals. H. L. Smith's case of buckwheat poisoning was described in 1909; Schloss' study in 1912 of a child sensitive to egg-white and to almonds is classical. Goodale's demonstration in 1914 that the application of horse dander to the turbinates causes an acute attack in horse asthmatics, and Talbot's further description of asthma in children susceptible to eggs were the precursors of a host of articles on similar subjects.

Incidence.—Asthma is common. Many of the clinics established for the study of this disease care for more than 100 patients a week. The condition occurs in individuals of all *ages* and *races*. The *sexes* are about equally affected, except that asthma as an accompaniment of chronic bronchitis and emphysema is rather more common in men over forty-five years of age.

Etiology.—The causes of asthma are manifold. They group themselves like the parts of a tree. The trunk represents a fundamental basis which may be called the "asthmatic state," which explains why some individuals have asthma and others do not. This trunk depends, perhaps, on several roots, one of which we recognize as inheritance, for it is known that in at least 50 per cent. of cases, some one in the family has had hay-fever, asthma, urticaria, or some peculiar susceptibility to a food or odor. The other roots are unknown. Upward the tree-trunk divides into two main branches: the first includes those individuals whose asthma is due to some cause outside of the body to which they are hypersensitive (the extrinsic group); the other includes those not demonstrably hypersensitive, where the cause is apparently inside the body (the intrinsic group). Reports of the relative percentage of cases in the two groups vary greatly: Cooke finds that 73.4 per cent. of patients belong in the extrinsic group, while Walker states that 40 per cent. is the correct figure, and Rackemann 31 per cent.

Extrinsic Asthma.—This is the disturbance set up in hypersensitive individuals by some foreign substance. That the hypersensitiveness may be acquired is shown by the cases in which there is industrial exposure to the offending substance and in which asthma develops only after repeated

exposure for months. Usually, however, asthma begins at the time of first contact.

Hypersensitiveness is manifested in at least two ways: (1) If, for example, an individual is hypersensitive to horses he has asthma whenever he comes in contact with a horse, the degree and duration of contact necessary to produce symptoms being proportional to the degree of sensitiveness. When away from horses such individuals are well. (2) When an extract of horse dander is placed on a scratch in the skin, (cutaneous test) or injected in high dilution into the skin (intradermal test) there is an immediate local reaction, which consists of an edematous swelling, pale in color, with sharp edges of irregular outline and surrounded by a bright red areola. When the extract is applied to the mucous membranes, itching with redness and swelling develops at once.

In extrinsic asthma contact with the foreign substance may be brought about by inhalation, ingestion, or direct exposure of the skin. Of these various methods inhalation is by far the most important in adults, while ingestion plays the important rôle in children. Direct contact through the skin is an unimportant cause of asthma, but is mentioned because certain drugs like novocain may produce eczema in some individuals.

Of the various proteins which may cause asthma by *inhalation* the *pollens* are the most important. That most frequently concerned is the pollen of ragweed, which throughout the United States is usually responsible for pollen hay-fever and pollen asthma of the autumnal type. That of timothy comes next in order and the other varieties of common hay which cause so much trouble in the early summer months. In the West, sage and cockleburr are important.

Danders and *emanations from animals* constitute another important group of etiological agents. An individual may be sensitive to one or several of the domestic animals or birds; sensitiveness to mice, rabbits, or guinea-pigs is less common.

A third group of proteins consists of various *vegetable dusts*. Some housewives have asthma when they mix bread; powders containing orris root may also cause trouble. A grocer may be sensitive to the dust of malt, hops, and so on.

Finally, a fourth group is composed of *miscellaneous dusts*. Cooke has called attention to the odor or dust of certain houses; and the dusts in certain industries are often factors. Leather dust, wool dust, urease, and glue fall within this group.

Asthma may follow the *ingestion* of certain *foods*. Egg-white with its chemical fractions is by far the most important cause of food asthma, especially in infants and young children. Next come the cereal proteins, especially wheat; then cow's milk. The miscellaneous group comprising a wide variety of foods and drugs contains no particularly important agent. Since the skin-tests are so often multiple, it is sometimes very difficult to prove clinically that one food is more responsible than another for the asthma, a fact which perhaps explains the confusing reports in the literature.

In general, we may say that dusts more frequently act as the causal agent of extrinsic asthma in adults while foods are more commonly the potent factor in children. Multiple sensitiveness, however, is the usual rule, and patients may be simultaneously sensitive not only to a pollen

and to an animal dander but also to some article of food, and all at the same time.

Intrinsic asthma is characterized by absence of hypersensitiveness to foreign proteins and is of several types. The symptoms appear to be referable to some cause within the body.

Bacterial asthma depends upon infection of the respiratory tract itself. There is a group of patients who have attacks of asthma quite regularly every spring and fall, each attack lasting for a few days or a week. The fact that these attacks are not preceded by change in environment, diet, or occupation makes it unreasonable to assume that any foreign protein is responsible and renders the diagnosis of "bacterial asthma" logical.

Asthma often follows common colds. Children frequently wheeze when their colds are severe. Such attacks may occur at intervals of a month or two without any change in diet or environment and are often called "asthmatic bronchitis," a term not without some merit.

Adults who suffer each winter with cough and dyspnea referable to emphysema and chronic bronchitis have attacks of real asthma when they "take fresh cold" and the cough becomes worse. It is clear that infection of the respiratory tract frequently acts as an aggravating cause of asthma.

Other Types of Intrinsic Asthma.—Intrinsic asthma also includes those cases in which the cause lies not in the respiratory tract, but in some other part of the body, or in some abnormal function of the body as a whole. This group of cases may be further subdivided according to the nature of the cause—reflex, toxic, or neurotic.

Reflex causes include certain disturbances in the nose or throat which produce asthma by direct irritation of the nerves, a possibility suggested by Sluder; and certain pelvic abnormalities—pregnancy, visceroptosis, and similar conditions.

Toxic causes include foci of infection which may be in the nasal sinuses, tonsils or teeth, or possibly in the appendix, gall-bladder, pelvis, or elsewhere. Asthma which clears up when a positive Wassermann becomes negative, or when diabetics become sugar free may also be included here.

Neurotic causes, in older treatises on asthma, are considered a very important etiological group. The history and symptoms in these cases are often so bizarre as to preclude at the outset any explanation other than a neurosis. On the other hand, it is astonishing how certain individuals who appear nervous and unreasonable become normal when more careful study eliminates the feather pillow, some toilet powder, or the household pet. In these cases the nervousness is obviously an effect of the asthma.

Nervousness, however, and the associated faulty hygiene may be in some cases the actual cause of asthma. The author recalls several children who have been relieved entirely by instituting such simple measures as the midday nap; a glass of milk between meals; less sympathy from the mother; or more out-door air even without any change in the diet, bedding, or environment. In adults, the onset of asthma occasionally coincides with a period of mental stress and strain and when thorough investigation fails to reveal another cause, such asthma disappears if the source of anxiety is removed.

Cardiac asthma and *renal asthma* are terms descriptive of the underlying cause in a few cases, but, as pointed out by Harkavy, diseases of the heart and arteries may co-exist with asthma, the cause of which is entirely sepa-

rate and independent. Whatever the original cause of asthma a *secondary infection of the bronchial mucous membrane* is prone to develop. Pollen asthma which ordinarily is relieved by the first frost of autumn may, because of a secondary infection, continue into the winter. Secondary bronchial infections are common in cardiac patients and may become the exciting cause of asthma which continues long after the circulation becomes normal.

Morbid Physiology.—Asthma is produced by a narrowing of the lumen of the bronchi probably throughout the entire bronchial tree, either by spasm of the bronchial muscles or by edema of the bronchial mucous membrane, or by both. The bronchi contain two sets of muscle-fibers, the constrictors and the dilators. Asthma is produced by overactivity of the broncho-constrictor fibers which may be stimulated either directly or through the vagus nerves which supply them. The dilator fibers are enervated chiefly by the sympathetic system; and the beneficial effect of epinephrin probably depends upon a stimulation of these broncho-dilator fibers which corrects the bronchiolar spasm and edema.

The mechanism by which asthma is produced is unknown. Its association with typical hay-fever, its close relation to the mucous membrane of the nose as shown by the frequent association of asthma and hay-fever, and by the relief which follows the removal of nasal polypi, or the use of an intranasal cocain spray, suggests some connection between the nerves of the nose and bronchi.

While direct extension of the exciting agent, pollen, horse dander, etc., down the respiratory tract is possible, it is more reasonable to conceive of an intranasal absorption of the protein which then reaches the lungs through the circulation. A similar conception would explain food asthma as the result of intestinal absorption.

Morbid Anatomy.—Death from asthma occurs so rarely that material for pathological study is scarce. Huber and Koessler have recently reviewed the 15 fatal cases reported in the literature and have added 6 more to the list. The pathological changes include hypertrophy of the bronchial glands and of the bronchial muscles with consequent definite thickening of the bronchial walls. Emphysema is always present, but in varying degrees in different portions of the lungs. Huber and Koessler find a certain parallelism between the clinical picture and the structural changes. One patient with asthma of a well-defined exudative type characterized by an abundant secretion showed a striking hypertrophy of the mucous gland system of the bronchi. In another case with an unproductive cough, the chief change was the hypertrophy of the smooth muscle system and the atrophy of the mucous glands. "The eosinophilic infiltration of the bronchial wall is a characteristic histological criterion of bronchial asthma," according to Huber and Koessler, "but if absent it does not exclude asthma" —in fact, "its constant absence in certain forms of bacterial asthma is regarded as one important part of evidence that there are types of asthma which may not be of allergic origin."

Eosinophilic cells in blood and sputum are characteristic of asthma. In the blood, the percentage may be as high as 50 or less than 2, regardless of whether the cause is extrinsic or intrinsic, and of whether the count is made during or between attacks. In the sputum they occur with considerable constancy in all types of asthma. The presence of eosinophil cells indicates that asthma is something more than a neurosis and suggests

a non-bacterial cause since eosinophils are characteristically increased by parenteral injections of protein. Charcot-Leyden crystals are so often associated with eosinophils that they have been considered by some authors as related not only to the cause of asthma, but to the eosinophilic cells themselves.

Symptoms.—*Bronchial asthma* is a syndrome of which the outstanding feature is wheezy breathing with obstruction to inspiration, expiration, or both. The severity and duration of this symptom, as well as its periodicity, vary with the cause. Between attacks of simple uncomplicated bronchial asthma, patients are subjectively and objectively well. For example, the patient with horse asthma goes into a stable. Within a few minutes his eyes begin to itch and smart, his nose runs and he sneezes; in another few minutes he coughs and experiences a tightness in his chest, with increasing difficulty in inspiration and expiration. The asthma thus induced may amount merely to an audible wheeze with no great discomfort, or it may force the subject to sit down with the elbows on the knees and the head down so that every accessory muscle of respiration can be brought into play. The breathing is slow, the phases, especially expiration, being long drawn out, and inspiration accompanied by obvious voluntary effort. Such extreme discomfort persists for minutes or hours depending on the degree of hypersensitiveness and the amount of protein absorbed. The patient may be well in half an hour or may wheeze for twelve or even twenty-four hours; when the attack is over, no symptoms develop as long as contact with horses is avoided.

Another type of asthma may come on at any time, with or without known cause. Attacks may be precipitated by exertion, cold air, dust or fumes, or may occur without any obvious reason. Sneezing and conjunctival symptoms are not common and the first symptom—wheezy, difficult breathing—is often promptly relieved by the use of some remedy. Individuals subject to these attacks are usually never without their "pet remedy" which may be a powder containing stramonium leaves, the smoke of which is inhaled, or some nasal spray containing cocain, or adrenalin. Such patients are uncomfortable at night. It is common for them to awaken from two to four times to burn their powder or take adrenalin. Occasionally they do not try to go to bed at all, but spend the night in a chair placed by a table over which they can lean and sleep between attacks.

The character of the *cough* varies. It depends usually on the amount of bronchial or tracheal infection. When there is little or no cough, the asthma is probably due to an extrinsic cause. It is characteristic of asthma, however, that at the end of each attack the patient coughs and raises sputum. When the paroxysm is over the bronchial secretion is set free.

The *sputum* varies in color, consistency, and amount, according to the degree and character of the secondary infection. Eosinophilic cells are characteristically present in the sputum of asthmatics. Curschmann's spirals about 1.0 cm. long can be seen with the naked eye. Charcot-Leyden crystals are elongated octahedra which vary in size from that of a red blood-cell to dimensions ten times as great. Both the spirals and the crystals are common findings, but their origin and significance is unknown. The bacteriology of the sputum varies widely. Cocci of various kinds are usually present in all specimens, but in general streptococci predominate in thin, watery sputum, while staphylococci, pneumococci, and influenza bacilli

are common in thick, yellow purulent sputum. In any specimen one organism may predominate, especially if the specimen is freshly obtained. Hemoptysis does not occur in simple asthma, but is not uncommon with the rupture of alveolar walls in emphysema. Pain in the chest is not characteristic and not common except as excessive cough produces a "sore chest."

Gastro-intestinal symptoms are rarely important. Patients cannot eat during a severe attack and loss of weight is consequently often marked. Abdominal pain occurs in a few patients susceptible to foods, but nausea, vomiting, and diarrhea are rare. Where there is much emphysema and chronic bronchitis, epigastric distress and belching of gas is common.

Physical examination between attacks shows that the subject is apparently normal in every way.

During an attack, musical, whistling, sibilant, or sonorous *râles* can be heard throughout the lungs. If the attack is subsiding, these râles may be emphasized by coughing. In severe attacks the *pulse* is often of poor quality: the pulmonic second sound is accentuated by the increased intrapulmonary arterial pressure, while the *heart* seems, on percussion, to be small, because of the distention of the overlying lung. *Cyanosis* is not present in patients with simple asthma, but may become very marked in those with considerable bronchial infection, particularly if there is a long-standing emphysema with a loss of elasticity of the bronchi and a coalescence of alveoli. Such patients suffer from a markedly increased dead space in their air passages and a greatly diminished vital capacity because of the large amount of retained air which they cannot expel. The *blood-pressure* is normal, but the systolic pressure falls sharply during inspiration, perhaps because of the increased negative pressure in the pleura during inspiration. Aside from eosinophilia, there are no important changes in the *blood*.

Diagnosis.—The diagnosis of asthma is usually made by the patient. Between attacks there is no evidence of asthma when there is no infection. During attacks, however, the wheezy dyspnea is so characteristic that diagnosis can be made on sight. The long arduous respiratory phases cannot be confused with the dyspnea of pneumonia or cardiac failure.

In determining the cause of asthma there are three important steps. The first is to discover the *circumstances under which the attacks occur*. With a good history a diagnosis of the cause, be it pollen, animal emanations, or some occupational dust, can often be made without further study. So, too, the association of asthma with respiratory infections may be so close as to rule out some extrinsic cause. It is often possible by the history alone to trace the development of advanced emphysema and chronic bronchitis through various stages to the original exciting cause—simple hay-fever.

The second step is the *physical examination*. Fever, cyanosis, purulent sputum, and râles which are clear cut and crackling indicate bronchial infection. Emphysema produces a percussion note and breath sounds which are characteristic. The bases of the lungs appear to be much lower and the heart outline much smaller than normal. Marked pallor and swelling of the nasal mucous membrane during the attack is typical in hay-fever and in asthma caused by hypersensitiveness to dust. All foci of infection, not only in the head but in the abdomen and pelvis, should be recognized promptly. Pregnancy, visceroptosis, malnutrition, especially in children, syphilis, and tuberculosis need only to be mentioned to empha-

size the importance of the recognition of such underlying causes as a preliminary to successful treatment.

The third step in diagnosis is the *skin test*. There are two methods of applying proteins and other foreign substances to the skin. The *cutaneous or scratch method*, advocated by Schloss and Walker, consists of the application of some of the protein in the form of dry powder to a drop of decinormal sodium hydrate solution on the arm and making a superficial scratch through the resulting solution. In the *intradermal method*, followed by Cooke, a sterile solution of the foreign substance in known concentration is injected between the layers of the skin. The powder or solution must give positive tests in individuals known to be sensitive to the corresponding substance and it must give no reaction in the skin of normal persons. With both methods a positive reaction produces, within twenty minutes, a pale urticarial wheal, with sharply defined irregular borders surrounded by a zone of bright erythema. When the wheals are small, with regular outlines, and appear about many or most of the scratches or points of injection, interpretation is difficult. It is the writer's custom to regard as positive only those tests which are in definite contrast to their neighbors. Both methods require accurate interpretation. The scratch method is easy to employ, the protein powders are relatively stable, and the results are usually clean-cut. The intradermal method is much more delicate and its results are more difficult to interpret, but when the reaction is negative, the lack of sensitiveness is practically proved.

Tests to be of diagnostic importance must be correlated with the history in such a way as to make a logical and reasonable explanation of the asthmatic attacks. Clinical experiments made either by changing the environment or by modifying the diet are frequently necessary before any positive tests can be of definite clinical importance. Many positive tests are found to be without clinical significance and cannot at present be explained.

Prognosis.—The prognosis as regards an immediate acute attack of asthma is good. Death rarely occurs during an attack, yet the author has recently reported 5 fatal cases of asthma, all quite similar to 3 of the 6 deaths from asthma described by Huber and Koessler and which define an important group. "The middle-aged well-nourished woman whose asthma has begun usually after the age of thirty, and which is at times severe; whose skin tests are negative; who is not relieved by admission to the hospital ward; and who may present evidence of some focus of infection, is very difficult to treat and carries a bad prognosis."

The hope of permanent relief from attacks of asthma depends entirely upon recognition of the cause, and upon the possibility of its removal.

Treatment.—The Attack.—The treatment of an attack is usually simple. Adrenalin chlorid injected subcutaneously can control almost any attack for a time varying from minutes to hours. A dose of 0.25 c.c. of 1 : 1000 solution often works as well as 1.0 c.c. The dose can be repeated at half-hour intervals if necessary. Dry epinephrin (1.5 mgm.) placed under the tongue is frequently efficacious, especially in children. As it is digested in the stomach it must not be swallowed. The inhalation of smoke of stramonium leaves, the chief constituent of most commercial asthma powders, and of asthma cigarettes, often relieves the bronchial spasm and the edema. Certain sprays for the nose and throat are also helpful. Steam,

plain or medicated with tincture of benzoin, may be inhaled. Atropin and belladonna paralyze the vagus endings and stop bronchiolar spasm. Morphin is not a specific and is rarely if ever indicated in the treatment of asthma. Benzyl benzoate is efficacious in a very few cases. Ephedrin, a Chinese alkaloid, has been shown by Chen and Schmidt to act like epinephrin, not only on hypodermic but on oral administration; and more recently MacDermot, and also Thomas, have used it successfully in asthma. The dose is 50 mgm. by mouth or subcutaneously. Whenever the attack is prolonged, the patient should be moved to new surroundings. Extrinsic causes of all sorts can usually be avoided by transfer to clean hospital wards. Special dust-free rooms ventilated by washed air, as described by Leopold and Van Leemven, are useful to rule out an extrinsic factor. Removal to a friend's house nearby or even to a different room and bed is often quite as effective as a change of climate.

The Cause.—Treatment of the underlying cause is of prime importance. A child with food asthma may be cured by elimination of the offending substances from the diet. A girl who is sensitive to a particular kind of face powder may be cured when she ceases to use it unless her roommate uses the same powder in considerable quantity. The laboratory worker sensitive to rabbits and guinea-pigs remains free from attacks as long as he stays away from the animal room.

A puzzling case of long-continued asthma of considerable severity ceased when the gall-bladder, containing a handful of stones, was removed. The extraction of bad teeth has brought complete relief from asthma in a few cases. A girl had her tonsils removed without any change in the asthma, but when later a chronic infection of both frontal sinuses was recognized and treated, the asthma practically disappeared for two years. It has since returned, however, in a mild form.

Inoculation with specific proteins in an attempt to reduce the degree of hypersensitiveness is a reasonable procedure, and may be desirable for two reasons: First, because of the difficulty of completely avoiding the offending substance, such as pollens during the hay-fever season or dusts in some industry; second, because of the persistence of symptoms in spite of almost complete avoidance of the protein in question. This type of treatment consists in a series of subcutaneous injections of the particular substance. The amount of the first dose is determined by applying small quantities of various dilutions to the surface of the arm and making scratches through them. That dilution which just fails to produce a positive reaction on the skin is selected for treatment. The first dose is small; succeeding doses must, in every case, be carefully regulated by the severity of the local reaction at the site of the previous injection, but in no case must a dose be much more than double the preceding dose, as the treatment is not without danger. General reactions following the hypodermic injection of proteins are not uncommon, and usually follow a large increase in the quantity injected. Such overdosage produces within a few minutes a marked urticarial reaction at the site of inoculation; this may soon be followed by general urticaria, wheezing, and, occasionally, by nausea, vomiting, and collapse. Death itself has been recorded. The injections are ordinarily given at intervals of five or seven days, often in a series of ten to twenty doses. At the end of the treatment the skin reaction is usually diminished, but it rarely disappears entirely. Since patients with ragweed hay-fever are not

benefited by injections of timothy, and as patients with cat asthma show no improvement after injections of horse-hair extract, desensitization is a highly specific phenomenon and can be successful only if the correct substance is used.

The treatment of intrinsic asthma with *bacterial vaccines* has become more common in the past few years. Direct indications for vaccines are few. Children who have attacks of asthmatic bronchitis at intervals should theoretically be much benefited by vaccines which produce a specific and active immunity against some particular micro-organism. Similarly in adults it should be possible to prevent recurring attacks by inducing an active specific immunity. Clinically, the author finds that the therapeutic value of vaccines in asthma varies directly with the severity of the local reaction which is produced by inoculation. Furthermore, the results with autogenous vaccines are not different from those with stock vaccines provided a similar local reaction is produced. This statement indicates that the therapeutic effect of any and all vaccines is probably non-specific. According to Rackemann's figures 77 patients out of a total of 131 were benefited by vaccines.

Treatment by *x-ray exposure* as advocated by Gerber has given relief to a few persistent cases when the degree of peribronchial thickening was marked.

The operation of *sympathectomy* is another procedure still in the experimental stage.

Potassium iodid has for years been successfully employed in the treatment of asthma. It is most helpful to patients with chronic bronchitis and emphysema. Some of these patients, however, must eventually be sent to a high dry climate like that of Arizona for relief. Iodids help children with "asthmatic bronchitis." *Ipecac* is also useful in these cases.

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ANGIONEUROTIC EDEMA

Definition.—Angioneurotic edema is characterized by transient, circumscribed, edematous swelling of the skin or mucous membranes, occasionally of the viscera. Individual lesions persist from a few hours to a few days

and may occur either without sensory phenomena or with itching, burning, or prickling sensations. One form is hereditary and frequently terminated by a fatal edema of the glottis; another form is relatively benign, and in some cases is dependent upon a demonstrable food allergy. Urticaria and angioneurotic edema are frequently associated.

History.—Under the title "akutes umschriebenes Hautödem" Quincke in 1882 described the non-hereditary form. Priority has usually been assigned to him, although Milton in 1876 described the same condition under the title of "Giant Urticaria." The first descriptions in American literature were from Osler, who reported a remarkable family history in which the disease was transmitted for five generations.

Incidence.—The condition is not rare. Bulloch in 1909 collected 170 cases from the literature. In six years there have been 47 cases in the wards and Out-patient Department of the Presbyterian Hospital, New York.

Etiology.—From Quincke's time belief in an *angioneurosis* as the important pathogenetic factor has persisted. Recent evidence makes it probable that in some of the non-hereditary cases the condition is due to *food allergy*. The offending food can, however, be discovered only exceptionally by skin reactions; these usually yield no helpful information. The *sexes* are about equally affected. No age is immune, but *onset* at puberty has been noted in numerous cases. The *hereditary form* of the disease may be transmitted through several generations by both affected and unaffected individuals without sex-linkage. The families studied do not show transmission according to the theoretical expectations of a Mendelian dominant.

Symptoms.—The swellings appear, as it were, spontaneously. An itching, prickling, or burning sensation may precede the appearance of a smooth rounded elevation varying in size from a few millimeters up to large areas covering nearly the entire back. The swellings may be tense and elastic or soft and pitting. The skin may not change in color over the swelling, or may become pink or dusky red. Areas commonly involved are the lips, the skin about the eyes, chin, hands, feet, and tongue, but any portion of the body surface may be affected. A swelling may persist several days, but more frequently disappears after twenty-four to thirty-six hours. There may be years between attacks, or edematous areas may appear almost daily for years. Involvement of the genitals has caused urethral occlusion. Visceral involvement, much more common in the hereditary form, may cause death by edema of the glottis. Gastro-intestinal crises with vomiting and abdominal pain have occurred in many familial cases. Cases simulating acute ileus, ruptured tubal pregnancy, appendicitis, acute cholecystitis, renal colic, and intussusception are on record. Fever may occur, but from available reports leukocytosis seems to be rare.

Associated skin lesions not infrequently observed are urticaria, erythema multiforme, and purpura.

Prognosis.—In the hereditary form the danger of death from edema of the glottis is serious. Of the 170 patients cited by Bulloch, 21.1 per cent. died in this way, and 67.9 per cent. of all the deaths were due to this lesion. In the non-hereditary form the prognosis is much better. Spontaneous cessation after a few months or a few years is to be expected. Edema of the glottis is rare in this group.

Treatment.—Except in the small percentage of cases in which a specific

allergy is found to be responsible for the occurrence of the swellings, treatment accomplishes little or nothing. In such patients elimination of the offending substance from the diet may prevent recurrences. Osler's statement that "treatment is very unsatisfactory" is still valid. Such nonspecific measures as administration of peptone, calcium lactate or chlorid, or autogenous defibrinated blood, and a variety of dietary restrictions, have also been found ineffective. Epinephrin and cold applications may be temporarily beneficial; tracheotomy may be required for edema of the larynx in the hereditary form. A concurrent acute infection often causes a temporary disappearance of the swellings. The most hopeful therapeutic procedure is to restrict the diet to one or two simple foods, such as rice and milk, for ten days or two weeks. The swellings may cease when the number of foods is thus limited. If one article of food is then added at a time three or four days after the previous addition, it is sometimes possible to observe that when a certain food is given the swelling reappears, and that when it is withdrawn the swelling disappears. In some patients it is possible to discover by this method the offending food and to prevent recurrence of the swellings by its elimination from the diet. Such treatment is, however, by no means always successful.

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DISEASES DUE TO PHYSICAL AGENTS

COMPRESSED AIR ILLNESS

(Caisson Disease, "The Bends," Divers' Palsy)

Compressed air illness is a condition produced in individuals who, after having breathed air under a pressure of considerably more than one atmosphere, are subjected to unduly rapid reduction of air pressure.

The disease was described in 1841 by Triger, a French engineer, who first employed a caisson in 1839. With the great increase in the use of compressed air in deep-water diving and in such engineering operations as pier construction and tunneling, numerous opportunities for the development of the malady occur.

Incidence.—In the construction of the East River tunnels (New York City) in 1909, 3692 cases of caisson sickness with 20 deaths developed in 557,000 decompressions from a maximum pressure of 42 pounds. In connection with the Public Service Commission tunnels, constructed in 1921, 1,361,461 decompressions resulted in 680 cases of the disease, with 2 deaths. The maximum pressure employed was over 47 pounds.

Etiology.—Workers entering a caisson pass through an airlock or chamber where the pressure is elevated to that of the working space. There may be some discomfort during this compression, because of pressure upon the tympanic membranes, but little danger. On leaving the caisson decompression also is effected in the airlock, and if the change takes place too rapidly, the atmospheric gases (nitrogen and carbon dioxid) dissolved in body fluids and tissues, which tend, in accordance with Dalton's law, to assume a lower pressure, may be liberated in the form of bubbles. It is these bubbles, mainly nitrogen, in nerve tissue, tendon sheaths, fascia, intestinal mucosa, and throughout the body which give rise to caisson disease.

There is little or no danger in rapid decompression from working pressures of 15 pounds[1] or less. At pressures above this, however, caution must be exercised to avoid over-exposure of workers to the abnormal conditions and to unduly rapid decompression. Various methods and rates of decompression have been proposed by Haldane and others and several states have elaborate regulations governing engineering operations which involve the use of caissons. Authoritative sources should be consulted for details regarding permissible limits of exposure to abnormal air pressures, and methods and rates of decompression.

Symptoms.—The more important evidences of compressed air illness, in order of frequency, are: (1) Localized pain in one or more extremities, or in the abdomen ("the bends"), which is the only symptom in about 90 per cent. of the cases; (2) vertigo ("the staggers"), which occurs alone or with other symptoms; (3) involvement of the central nervous system, monoplegia, or diplegia, due to cerebral irritation or sensory and motor disturbances attributable to the presence of gas bubbles in the spinal cord; (4) dyspnea ("the chokes"); and (5) collapse and unconsciousness. The onset of

[1] A gage pressure of 15 pounds represents pressure above that of a single atmosphere.

symptoms in about 50 per cent. of the cases occurs within thirty minutes after decompression; in 90 to 95 per cent., within three hours.

Prognosis.—If promptly and properly treated the chances of complete recovery are excellent. Cases untreated for several hours after the onset of symptoms are not so favored. Recovery after collapse is doubtful.

Treatment.—Treatment of caisson disease is essentially recompression. The subject should be placed at the earliest possible moment after the onset of symptoms in a steel chamber or "medical lock," where he is subjected to the same pressure from which he was originally decompressed. When the bubbles distributed throughout the body have been taken up, decompression may be slowly effected. Acute caisson disease should not be treated in hospital wards or at home. Medical treatment is of little value.

WADE WRIGHT.

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MOUNTAIN SICKNESS

The ascent to high altitudes of persons accustomed to living under the pressure of practically an entire atmosphere (760 mm. of mercury) frequently produces distressing and possibly serious consequences.

The effects of diminished atmospheric pressure may be manifested very quickly if the ascent be rapid, as, for instance, in aëroplanes or balloons; or more gradually during the ascent of mountains. In individuals who reside permanently in rarefied air there may be structural as well as functional adaptive changes. Few persons possess such powers of adaptation that they do not suffer at least some discomfort on ascending more than 12,000 feet above sea level.

The essential adaptations to rarefied air, which are due to the lowered oxygen pressure, involve the blood and the cardio-respiratory mechanism. According to Barcroft and his associates, who went to the Peruvian Andes in 1922, the principal factors in acclimatization are: (*a*) an increase in the pulmonary ventilation which results in an increased alveolar oxygen pressure; (*b*) a shift in the oxygen dissociation curve which increases the capacity of the hemoglobin for oxygen; and, (*c*) an increase in the number of red blood-cells and in the hemoglobin, without change in the color index. At high altitudes there was an increase in the number of reticulated red cells, but no nucleated red cells were seen.

Contrary to previous conceptions, Barcroft found that at 14,000 feet the blood of a resting individual was not abnormally alkaline. During

exercise the rise in hydrogen-ion concentration was greater than at sea level. He considered the increased respiratory activity to be due to the effect of an insufficiency of oxygen on the respiratory center.

Symptoms.—The symptoms of mountain sickness differ in kind and severity in different individuals and at different altitudes. Headache—usually frontal—vertigo, malaise, mental dulness, abnormalities of vision and hearing, epistaxis, nausea, vomiting, cyanosis, dyspnea, palpitation, and muscular weakness are commonly noted. There may be a slight fever. Respiration is labored. The pulse may be slightly accelerated and the systolic blood-pressure very moderately raised.

With rest some degree of accommodation is ordinarily acquired within a few days. Oxygen affords prompt relief.

In aviators flying above 12,000 feet dyspnea is common. As the altitude is increased headache, muscular weakness, apathy, and psychic disorders may be manifested. An altitude of 25,000 feet is considered the utmost limit to which an aviator may safely ascend without recourse to the use of oxygen. In mountain climbing the effects of diminished pressure may be observed at much lower altitudes because of the usual association of rarefied air and more or less severe physical exertion.

While balloonists have apparently died because of oxygen want, the effects of diminished atmospheric pressure upon persons of normal cardio-vascular mechanism are ordinarily those previously described. Individuals suffering from cardio-vascular disease are, of course, at a peculiar disadvantage, and in them the effects of the rarefied atmosphere are correspondingly intensified.

Treatment.—To relieve the oxygen want oxygen should be given. For the fatigue and the psychic disturbances often incurred by aviators the treatment is rest.

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HEAT EXHAUSTION AND HEAT-STROKE

Numerous industrial workers (stokers, smelters, roofers, miners, and certain iron and steel workers) who are at times exposed to extreme heat may suffer not only the superficial effects of radiant heat, but from the more severe manifestations of exhaustion, heat-stroke, or, more rarely, of heat cramps.

Exposure, such as to the heat of fire-rooms, of deep metal mines, particularly with high humidity, may induce exhaustion with pronounced physical weakness, dizziness, stupor, pallor, profuse perspiration, slight or

moderate increase in body temperature (but often a subnormal temperature), acceleration of the pulse rate and of respiration, and a lowering of blood-pressure. Occasionally manifestations of this nature are associated with severe cramping pain in the muscles of the abdomen or of the extremities. Ordinarily the subjects do not lose consciousness.

In *heat-stroke* or *sunstroke* the heat-regulating mechanism of the body is apparently overwhelmed and not merely embarrassed as in heat exhaustion. The onset may be catastrophic, with almost instantaneous death, or there may be premonitory headache, dizziness, nausea, and visual disturbances.

Consciousness is lost early in the course of the attack. The face of the patient is flushed, the skin dry and hot. The body temperature is elevated in the more severe cases to 109° F. or more. In the first stages of heatstroke the pulse is full and rapid, the breathing deep, and the pupils possibly dilated. As the patient's condition becomes progressively worse the pulse grows irregular, rapid, and more feeble, the breathing more shallow and of the Cheyne-Stokes type, and the pupils contract.

Heat exhaustion may readily be distinguished from heat-stroke when well defined, but differentiation under conditions of industrial medical practice is not always easy. It is, consequently, important to observe the temperature and cardiac function carefully.

Osler and McCrae direct attention to a condition prevalent in the tropics and in the Southern states, which lasts several days, is characterized by fever and weakness, and is considered to be due to heat exhaustion.

Death from heat-stroke may occur within a few minutes, but if the patient survives the second day, recovery is probable. Persistent susceptibility to heat and impairment of memory are commonly noted after severe attacks of heat exhaustion or heatstroke.

Treatment of *heat exhaustion* usually calls only for rest in a cool place. If it is severe, stimulation may be necessary to offset the notable depression, and cooling sponges or warm baths to favor return of the temperature to normal. Most antipyretic drugs should be avoided or used with caution.

Heat-stroke demands prompt and often heroic treatment. Ice-water baths, cold sprays, ice packs, and ice-water enemata may be used until the body temperature is reduced to about 102° F.; cold sponges may then be used. The heart should be carefully watched, and if evidence of marked pulmonary congestion appears, venesection should be performed.

Edsall has described recurrent attacks of muscle spasm among persons exposed to high heat. The onset is usually sudden. The spasms involve successively groups of muscles of the extremities or of the abdominal wall; and may occur intermittently for twenty-four hours, seldom longer. Edsall considered the condition to be of toxic origin, and not the result of dehydration. Treatment is symptomatic, rest, warm baths, and sedatives being of value.

WADE WRIGHT.

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ELECTRIC SHOCK

Though most cases of serious electric shock result from contact with currents of relatively high voltage, deaths have occurred after exposure to voltages well below those ordinarily used on lighting circuits. It is, accordingly, of great importance that information regarding methods of resuscitation of victims of electric shock be widely disseminated.

Shock may result when an individual becomes a part of the path of flow of current between poles of varying potential. With direct current the flow is in a single direction, with alternating current the direction is frequently reversed, the frequency being expressed as cycles per second. Fatal shock seldom results from contact with a direct current of less than 300 volts, but the danger increases with the voltage. Alternating currents, if of few cycles (15 to 60), may cause death in well-grounded subjects, even at the 110–115 volts commonly employed for home lighting, but alternating currents of high voltages if of high frequency may be handled with relative safety. Broadly speaking, currents of less than 25 milliamperes are not dangerous.

The tendency of direct current of low voltage is to arrest the heart without affecting the respiration. Alternating currents of low tension throw the heart into fibrillation. High-tension currents may arrest respiration and not at once affect the heart. It is not possible to generalize about the action of currents of moderate tension, as much depends upon the length of contact, upon skin resistance, and the path which the current takes through the body. Much remains unknown concerning the mechanism of electric shock and the mode of death.

Moist skin, wet clothing, contact with wet ground, all favor electrical contact. Untoward effects are particularly likely to occur if the thorax is in the path of the current, as, for example, when contacts are made with the right arm and left leg. High-tension currents may possibly be borne without fatality if the contacts are effected through one arm and a leg of the same side or both legs. This fact bears upon the importance of exercising care in endeavoring to free a victim from live contacts.

Morbid Anatomy.—The *postmortem* evidences of electrocution are variable. Extensive charring may mark the points of entrance and exit of the current, or the burns may be slight, or, at times, absent. The superficial effects of direct currents are usually more marked than those of alternating currents. The blood is often dark and rarely coagulated. Minute hemorrhages are found in some cases in the brain and cord.

Symptoms.—Loss of consciousness and burns of varying degree are the outstanding evidences of electric shock. Death may be instantaneous or result after seconds or hours. During recovery consciousness may be regained shortly after shock or not for several hours. Restlessness and dilatation of the pupils are common.

Because of the tendency to electrolysis of deep tissues the possibility of secondary hemorrhage must be kept in mind in connection with the treatment of cases involving extensive burns. It is common for those who recover from electric shock to suffer various after-effects, such as headache and nervous irritability. These are considered to be essentially psychic in origin.

Treatment.—Once the victim is freed from the current, artificial respira-

tion is the one measure first necessary in the treatment of electric shock, whether there is cardiac or respiratory failure.

The commission on resuscitation, representing the American Medical Association, the National Electric Light Association, and the American Institute of Electrical Engineers, recommends the Schaefer method of artificial respiration, and advises that it be continued for at least four hours unless normal respiration has been previously restored.

WADE WRIGHT.

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DISEASES DUE TO CHEMICAL AGENTS

CARBON MONOXID POISONING

Acute poisoning by carbon monoxid (CO) may result from the inhalation of an atmosphere containing as little of the gas as a few hundredths of 1 per cent.

Carbon monoxid is produced by the imperfect oxidation of carboniferous material, and is probably the most widely distributed of all toxic agents. It is encountered in the steel industry, in coal mining, in processes utilizing gas heat, in connection with the use of explosives in confined spaces, in smoke, and very commonly in the exhaust of internal combustion engines. Coal gas contains about 16 per cent.; blast furnace stack gas, 28 per cent.; mine air after dust explosions, 1 per cent. or more; and the exhaust from automobile motors about 7 per cent. Carbon monoxid is colorless and, in ordinary concentrations, odorless.

Incidence.—Exact statistics regarding the incidence of poisoning are not to be had, for without doubt thousands of persons are daily affected to some degree by the gas. Serious, even fatal poisoning, however, is so common as to warrant continued popular education regarding the menace.

Etiology.—Carbon monoxid has an affinity for hemoglobin approximately three hundred times that of oxygen. The reaction is, however, reversible and depends on the relative tensions of CO and of O in the aveolar air, a fact of importance in treatment.

The following table, prepared by Sayers and Yant, shows the length of time required for various concentrations of CO to saturate the blood to 80 per cent. of full equilibrium:

Concentration of carbon monoxid in air (inclusive).	Percentage saturation of blood (80 per cent. of approximate equilibrium values).	Hours.	Minutes.
0.02–0.03	23–30	5 –6	
0.04–0.06	36–44	4 –5	
0.07–0.10	47–53	3 –4	
0.11–0.15	55–60	1½–3	
0.16–0.20	61–64	1 –1½	
0.20–0.30	64–68		30–45
0.30–0.50	68–73		20–30
0.50–1.00	73–76		2– 5

The development of poisoning thus depends upon the concentration of CO and the time of exposure.

Morbid Anatomy.—In *postmortem* examinations after death from CO poisoning the blood is a bright cherry red, and the various lining membranes are red or show ecchymoses. Punctate hemorrhages and edema of the brain are common.

Symptoms.—A chronic form of poisoning is believed by many authors to be characterized by headache, palpitation, anemia, vertigo, and, in some cases, polycythemia. There is a striking variation in individual susceptibility to the poison, and very probably a gradual adaptation.

Carbon monoxid is harmful in that it produces anoxemia. Death is due to respiratory failure. The gas is not an irritant or in itself specifically toxic.

The effect of inhalation of CO is first stimulation and later depression of centers controlling respiratory and cardio-vascular activity. Headache is usually the earliest symptom and may appear when the percentage saturation of the blood is very low. As the blood becomes 25 per cent. saturated headache may be severe, and be associated with vertigo, muscular weakness, psychic disturbance, failure of vision, and gastric distress. With increasing saturation there may be collapse, and rapid or, at times, intermittent respiration, acceleration of the pulse, and possibly convulsions. In later stages coma, convulsions, and weakness of the pulse and respiration may develop.

Death is likely to occur if the per cent. saturation of the blood rises to 70 or 80. In severely gassed patients pneumonia frequently develops. A great proportion of the hospital patients with CO poisoning have fever and marked leukocytosis.

Henderson presented in connection with the study of the exhaust system for the New York-New Jersey vehicular tunnel the following observations:

"1. When the time of exposure in hours times the concentration of carbon monoxid in parts per 10,000 equals 3, there is no perceptible effect.

"2. When the result is 6, there is just a perceptible effect.

"3. When the result is 9, there will be headache and nausea.

"4. When the result is 15 or more, the conditions are dangerous to life.

"5. If the volume of breathing is increased by exercise (even by slow walking, and correspondingly more by physical work) the rate of absorption of carbon monoxid is increased proportionally."

There are in the literature descriptions of numerous cases of continued psychoses, of amnesia, and of visual disturbance following exposure to CO. Delayed secondary effects, such as cerebral hemorrhage and paralysis, have also been observed some days after apparent recovery. When the coma continues for a day or more the prognosis is not favorable.

Diagnosis.—Absolute diagnosis is dependent on the identification of carbon monoxid hemoglobin. The pyrotannic acid method perfected by Sayers, Yant, and Jones permits reasonably accurate quantitative estimation of the quantity of carbon monoxid in the blood or air.

A very sensitive method for the estimation of carbon monoxid in air has been perfected by Teague (oxidizing CO with iodin pentoxid).

Treatment.—The emergency treatment of gassed patients requires immediate *artificial respiration,* if breathing has ceased, preferably by the Schaefer method. Mechanical devices are not to be advocated.

The *inhalation of pure oxygen* greatly accelerates the release of CO from the hemoglobin—about four or five times as rapidly as does pure air—but a 5 per cent. mixture of carbon dioxid in oxygen is, according to Henderson and Haggard, even more effective. In patients promptly treated with this oxygen-carbon-dioxid gas mixture the blood may be practically freed of CO within half an hour. Severely poisoned individuals after receiving emergency treatment should be given hospital care if possible.

WADE WRIGHT.

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BRASS POISONING

No poisoning is now attributed to the action of brass. "Brass founders' ague" is thought to be caused by the inhalation of fumes of zinc in the form of zinc oxid, and is characterized by chills, fever, sweating, and shivering.

Incidence.—It was first described by Thachrah in 1832, and is commonly known among brass foundrymen. It not only develops in individuals in contact with fumes from molten brass, but occurs also among zinc smelters, scrap metal refiners, makers of zinc oxid, galvanizers, and men who work with zinc heated to such a point that fumes are given off and oxidized. Only those exposed to the oxid in its fresh state are affected. The inhalation of zinc oxid as commercially distributed is without effect. Other metals such as copper, nickel, and cadmium are said to produce similar maladies. There is no evidence that any chronic poisoning is produced by zinc.

Etiology.—Though the true nature of the disease is not explained, the changes are thought to be due to a destruction of protein in the respiratory passages, which produces a reaction akin to anaphylaxis.

Symptoms.—After several hours' exposure to the oxidized fumes of zinc (for the susceptible, even an exposure of a few minutes suffices) there develops a sense of dryness and burning in the upper respiratory passage. Headache, cough, languor, possibly nausea and vomiting ensue. Within a few hours the subject feels chilly, begins to shiver, and in most cases is obliged to go to bed. The chill may last for an hour or more and is unrelieved by external application of heat. The pulse tends to be rapid, the respiration unaffected. The temperature may rise moderately, remain normal, or fall.

The distressing symptoms end abruptly, the patient perspires copiously, sleeps, and is ordinarily able to return to work; slight weakness is perhaps the only after-effect.

Following an attack, albumin is present in the urine for a day or two. Zinc is excreted in the urine and feces.

Some degree of immunity apparently exists in about 75 per cent. of exposed workers, according to Hayhurst, and about 20 per cent. are affected occasionally. The incidence of the disease is related, in a measure, to the nature of the alloys used (large proportions of zinc increase the frequency), to foundry ventilation, and to external temperature (cold air serves to precipitate the chills).

Diagnosis.—The diagnosis is determined essentially by knowledge of exposure to fumes of zinc, by the abrupt recovery from attacks, and by the absence of important sequelæ.

Prognosis.—Recovery is usually almost complete within a day, and workmen view the disease so casually that frequently they do not seek medical assistance. Relatively few physicians ever see zinc ague in the acute stage.

Treatment.—There is no specific treatment.

WADE WRIGHT.

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BENZOL POISONING

The inhalation of fumes of benzol (coal-tar benzene, C_6H_6), has frequently produced serious poisoning. Benzol as it is utilized commercially usually contains small amounts of other coal-tar derivatives, such as xylol, toluol, and thiophene, substances considered much less toxic than benzol.

Benzol is at the present time quite widely employed in industry. Workers are exposed to the substance in connection with the distillation of coal-tar, in the manufacture of motor fuels to which benzol is added, in many chemical industries, in certain processes in the rubber industry, and in the manufacture of cans, particularly those with a rubber or composition seal. The present wide-spread use of lacquers and paints applied with spray guns has greatly increased the industrial exposure, for many of the painting materials used contain important quantities of this substance.

Acute poisoning may result from exposure to high concentrations, and death may ensue after a few moments from the respiratory failure which follows a brief interval of successive dizziness, profound weakness, and unconsciousness. Of more frequent occurrence is a *subacute type* of poisoning manifested after days or even months of industrial contact with benzol. A severe and rapidly progressive aplastic anemia is produced, which in many instances is accompanied by profuse hemorrhage and results in death. The evidences of disease may be so slight and develop so slowly as to warrant classification of the condition as chronic.

It has been found that a concentration of 15 parts of benzol per 1,000,000

of air may in some hours produce slight effects, while unconsciousness may be produced in susceptible individuals by 20 or 30 parts per 1,000,000. These limits are quite below those often encountered in industry, but it is now held that 200 parts per 1,000,000 should not be exceeded in any working space.

Symptoms.—The symptoms and signs in the moderately acute form vary from asthenia, headache, and gastro-intestinal changes, with possibly a moderate leukopenia or slight epistaxis, to great weakness, with a very marked anemia (the red blood-cell count reduced to less than a million and the leukocyte count to several hundred per cubic millimeter), and hemorrhages into the skin and from the mouth, nose, and gastro-intestinal and uterine mucosa.

Diagnosis.—The occurrence of a definite leukopenia in connection with exposure to benzol should certainly be considered presumptive evidence of poisoning.

Prognosis.—Many severely poisoned patients die after several days or weeks, others have recovered after prolonged illness. The mortality for cases of this nature has in the past been about 50 per cent. or higher.

Treatment.—The most important measures which control the disease are the provision of adequate ventilation in industrial plants where benzol is used, and periodic examination of the blood of exposed workers which permits prompt removal of even slightly affected individuals.

For patients suffering from hemorrhage *transfusion* is necessary. In numerous instances, indeed, only repeated transfusion has saved the patient's life. In cases overcome acutely, artificial respiration and use of oxygen may be indicated. Other treatment is symptomatic.

WADE WRIGHT.

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ARSENIC POISONING

Arsenic poisoning results usually from exposure to one of the oxids of arsenic, particularly to arsenious acid anhydrid (As_2O_3), or to arsenical salts, such as Paris green (aceto-arsenite of copper), or lead arsenate. Arseniureted hydrogen (arsin, AsH_3) is highly toxic, but produces effects quite different from those of arsenic oxids. Pure metallic arsenic is considered harmless.

Incidence.—Most *industrial arsenic poisoning* is seen in workmen engaged in extracting white arsenic (As_2O_3) from cobalt and arsenical

pyrites by roasting the ore; in the manufacture of arsenical salts and products; in the preparation of sheep dip, a mixture of white arsenic, sulphur, and a caustic alkali; or in handling skins treated with arsenic. *Non-industrial poisoning*, caused by the arsenical dyes in paper or fabrics, is now practically unknown.

Etiology.—Poisoning by *arseniureted hydrogen* has occurred principally in chemical and galvanizing works. It may be produced when an acid and a metal, either or both containing arsenic, are brought in contact with a resulting liberation of nascent hydrogen which combines with arsenic to form the toxic gas. Poisoning has occurred among members of the crews of submarines because of the arsenic in storage battery plates, and on ships, carrying ferro-silicon, which in contact with air and moisture tends to decompose and liberate arseniureted hydrogen.

Arsenic oxid and the salts are local irritants to the skin and the mucous membrane of the mouth and respiratory passages. Inhalation or ingestion of their dust produces local and systemic changes. Acute poisoning rarely occurs in industry and is usually due to the use of arsenic for suicidal purposes. One grain (65 mgm.) of *arsenic trioxid* has proved fatal. Though the normal therapeutic dose of this substance is 2 mgm., the "arsenic eaters" of Styria can safely take over 400 mgm. twice a week.

The inhalation, over a moderate period, of arseniureted hydrogen in a concentration of 3 parts per 100,000 may produce symptoms. Death may follow inhalation of 0.3 to 0.6 gm. of the gas.

Morbid Anatomy.—Delepine has reported that after poisoning by arsenic trichlorid there is granulofatty degeneration of the heart, liver, kidneys, pancreas, and gastric and duodenal glands.

After death from poisoning by As_2H_3 the liver has been found to be large and edematous, with some evidences of fatty degeneration; the kidneys large, and the renal epithelium degenerated and necrotic.

Symptoms.—Arsenic oxids, or salts as dusts, produce superficially a *dermatitis* or even *ulceration* about folds of skin, as in the axillæ or about the scrotum. Increased *pigmentation* may be noted about the axillæ, the nipples, the eyelids, and on the neck. *Keratosis* of the palms and soles may develop after prolonged ingestion of arsenic, and *skin cancer* has been reported to follow the use of the drug. *Scleroderma* was found by Ayres to be associated with exposure to arsenic and to occur in patients who were eliminating arsenic in the urine.

The *septum of the nose* is in some cases perforated. Legge states that the margins of the cartilage are not involved, and that perforation, due to arsenic, may be thus differentiated from syphilitic perforation.

Other symptoms are edema of the lids, coryza, pharyngitis, and laryngitis. With more serious poisoning, vomiting, abdominal pain, and diarrhea may be marked. A peripheral neuritis with pronounced paresthesia is moderately common. Paralysis similar to that produced by lead may result from the absorption of arsenic, the legs being more notably affected than the arms.

Poisoning by arseniureted hydrogen is manifested usually a few hours after the gas is inhaled, first by nausea and vomiting, then by headache, vertigo, and increasing weakness. Severely poisoned patients show intense jaundice, dusky mucous membranes, edema of the face, and conjunctivitis. The liver is tender, albuminuria develops, and possibly hemoglobinuria or

hematuria. The blood is strikingly affected. In Dudley's series of 30 moderately severe cases, occurring in submarine crews, the red cells were markedly reduced; in 2 cases the count was less than 2,000,000; the leukocytes were not apparently involved. The hemoglobin content of the blood was low, but in marked cases there was a high color index, marked degeneration of the red cells, and erythroblasts, particularly of the megaloblasts.

Diagnosis.—The diagnosis is facilitated by careful inquiry into the nature of the patient's work and by chemical examination of the urine.

Prognosis.—Industrial poisoning by arsenical oxid or salts is rarely fatal. Manifestations of the disease may persist for weeks or months.

Poisoning by arseniureted hydrogen, if severe, is usually fatal within about a week, death being due essentially to destruction of blood.

Serious damage to the kidneys is inevitable and impairment of the renal function complicates recovery. Mildly poisoned patients recover.

Treatment.—*Chronic poisoning* by arsenic is treated by promoting elimination through the kidneys and bowels.

In poisoning by arseniureted, hydrogen oxygen should be promptly administered and the inhalations prolonged. Transfusion may be necessary.

WADE WRIGHT.

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MERCURY POISONING

For centuries mercury has been used in the arts, and both the metal and many of its salts have been employed therapeutically. Paracelsus (1493-1541) advocated its use for the treatment of syphilis, and Mead (1673–1754) recommended the swallowing of the metal "to a pound weight at least," in cases of "iliac passion" in order that by its ponderosity it might restore the natural motion of the intestines.

Acute Poisoning.—ETIOLOGY.—Acute poisoning is usually caused by ingestion of bichlorid of mercury, accidentally or with suicidal intent. The absorption of mercury administered therapeutically by mouth, injection, inunction, or in vaginal douches less frequently produces the acute or subacute type. Ingestion of 0.1 gm. or even somewhat less of mercuric chlorid may result in acute poisoning, although usually 1 gm. or more is required to render the condition serious.

SYMPTOMS.—Mercury is quickly absorbed from the stomach and becomes widely distributed throughout the body. The onset of symptoms is usually rapid: within a few minutes after ingestion *abdominal pain* develops, especially in the epigastrium. This is, fortunately, in most cases associated with *vomiting* which allows rejection of a portion of the ingested poison.

There is a *metallic taste* in the mouth, often a marked *stomatitis* and *congestion of the pharynx and esophagus.* The vomitus may early contain blood-streaked mucus. Loose, bloody *stools* are passed before long. There may be early collapse, and, in exceptional cases, delirium and convulsions.

Blood and Urine.—Examination of the blood of patients with mercury poisoning during the first few days shows that nitrogen is retained, the concentration of the whole blood chlorids reduced, and the alkali reserve lowered. The phthalein test ordinarily indicates a low renal function. The urine is commonly strongly acid to methyl red. As the patient improves these abnormalities disappear.

Prognosis.—Although unusually severe poisoning may prove fatal within an hour, death seldom occurs for several days. Prompt and thorough therapy has reduced the mortality of patients treated in hospitals during the past decade to less than 6 per cent.

When the intoxication is not promptly fatal, signs of gastro-intestinal inflammation and striking evidence of injury to the kidneys usually continue. Albumin, casts, and blood appear in the urine a few hours after ingestion of the poison, and suppression of urine, possibly complete anuria, is soon noted. This marked diminution of urinary secretion renders the condition very similar to the uremia of chronic nephritis. There may be headache, coma, and edema. MacNider concluded from his detailed experimental studies of mercury poisoning that when death is not associated with massive poisoning and very severe gastro-enteritis, it is due to damage to the kidneys characterized by an acute swelling and necrosis of the renal epithelium. These changes are not, however, caused by the action of mercury in the course of elimination, but are attributable to an acid intoxication.

Treatment.—The treatment described by Weiss is devised to overcome the effects produced by the poison rather than to provide an antidote to mercury. It may be outlined as follows:

> The stomach is immediately washed with a saturated solution of sodium bicarbonate, the operation being continued until the washings are clear. At least 2 liters of the solution should be used. Before withdrawing the stomach-tube 6 ounces of a saturated solution of magnesium sulphate are administered. A soapsuds enema is then given. As soon as possible thereafter an alkali should be injected intravenously (Fischer's solution, crystalline sodium carbonate 10 gm., sodium chlorid 15 gm., distilled water 1 liter; or a 4 per cent. solution of sodium bicarbonate) in quantities as large as 1000 to 1800 c.c. if there is no disturbing cardio-vascular disease. Second or third injections should be given on successive days if more than 0.5 gm. (7½ gr.) of mercuric chlorid was ingested or if there is striking evidence of renal injury.
>
> From the onset, a beverage made by dissolving 4 gm. (1 teaspoonful) of potassium bitartrate and 2 gm. (½ teaspoonful) of sodium citrate in a glass of water, orangeade, or lemonade is to be administered six to eight times daily. Weiss has seldom used rectal irrigation or hot packs. He permits a liberal diet after diarrhea ceases.

The treatment is controlled by urinalysis and an effort made to keep the urine alkaline to methyl red. Albumin, casts, and blood after a few days diminish and clinical recovery is usually effected in twelve to fifteen days.

The use of calcium sulphid intravenously as an andidote has been proposed, but its efficacy is very doubtful.

Subacute poisoning is ordinarily caused by the excessive therapeutic use of mercury. The common symptoms—salivation, gingivitis, and diarrhea—subside upon the withdrawal of the drug.

Industrial Poisoning.—Industrial mercury poisoning is almost invariably

a chronic intoxication resulting from the inhalation of volatilized mercury for a long period. The most hazardous trades are the production of mercury and its derivatives, the manufacture of scientific apparatus (thermometers and barometers), the preparation of hatters' fur and felt hat making, the extraction of gold and silver by amalgamation, and the preparation and handling of the fulminate of mercury used as a detonator of explosives. The daily absorption of approximately 1 mgm. for several months may produce symptoms of poisoning, although most intoxications, particularly in the hat industry, becomes apparent only after many months or several years of exposure.

Symptoms.—Chronic mercurialism has various manifestations, far from all of which may be observed in any one case. The most typical symptoms are included in the first three of the following groups:

1. Stomatitis, salivation, a metallic taste, reddish-brown discoloration of the buccal mucosa, gingivitis, loosening of the teeth, and occasionally a marking of the gums similar to the lead line.

2. Erythismus mercurialis, a peculiar psychic disturbance characterized by ready excitability and a strange shyness in the presence of strangers, a symptom of great interest and importance; insomnia; headache; vertigo; mental depression and dulness; and, rarely, hallucinations.

3. Tremors of the orbit, lips, tongue, fingers, and limbs. These are usually moderately fine at first, but at intervals become a coarse jerking. They may become very severe and in rare instances involve contractions of the limbs of such violence as to require restraint. The tremor is intentional and subsides during rest. Under observation it may increase and diminish, rhythmically recurring. When it is marked, the patient may require assistance in eating and in other activities. Weakness of both the flexor and extensor muscles of the hand and forearm has been reported, but marked paresis is rarely, if indeed ever, caused by mercury. Polyneuritis is said to result occasionally from exposure to mercury. There is no ataxia and the reflexes are not notably affected.

4. Albuminuria and high blood-pressure. While the severe nephritis associated with acute mercurial poisoning is not associated with the chronic type, these symptoms appear with such frequency as to warrant the belief that the kidneys are usually involved in chronic poisoning.

5. Loss of appetite, indigestion, and diarrhea are occasionally observed. There is loss of weight in severe cases. The blood is normal except for a moderate secondary anemia.

Dermatitis characterized by erythema and desquamation is not uncommonly produced by contact with mercuric chlorid or even by ingestion of mercury. In susceptible individuals fulminate of mercury produces severe dermatitis. Punched-out and penetrating ulcers may develop about the finger-nails and knuckles. The conjunctivæ and the mucous membranes of the mouth, nose, and larynx are often affected.

Prognosis.—There is apparently no acquired immunity to mercury. The severity of symptoms is usually determined by the length and degree of exposure to the poison. While most severe symptoms tend to decrease when the subject is removed from contact with mercury, such manifestations as erethism and tremor may persist for a long time. Tremor particularly has been observed many years after the last exposure. Chronic mercury poisoning is only indirectly a cause of death.

Treatment should eliminate the metal through the bowels, kidneys, and skin. The symptoms are relieved by suitable hygiene.

Mercury dermatitis may be prevented and to some degree relieved by application of a 10 per cent. solution of sodium hyposulphite. A 2 per cent. solution may be used as a wash for conjunctivitis.

Wade Wright.

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LEAD POISONING

Ever since lead has been used in industry and the arts lead poisoning has been a well-known occupational disease. Physicians of the Middle Ages associated colic and anemia with the poison, but to Tanquerel des Planches (1831) belongs the credit of first correlating all the manifestations of the intoxication. It is now known that the blood, striated and smooth muscle, and the nervous system are most strikingly affected, and that the disease is usually associated with inhalation of the dust of lead or of its compounds, and with the ingestion of contaminated foods and liquids.

Incidence.—Although lead poisoning is still the most important of all industrial diseases, the relative frequency of occurrence is far lower than it was fifteen years ago. The recent work of Oliver and Legge in England and of Alice Hamilton in America has proved that prevention is possible; and as a result of the legislation and factory improvement incited by their investigations the number of cases in industry is rapidly declining. About one hundred and fifty industries involve some exposure to lead. The dusty trades are the most hazardous, and include the manufacture of white and red lead, of storage batteries, and of pottery, as well as painting, printing, and the mixing of rubber.

Etiology.—Outside of industry lead poisoning is infrequent. Recently the preparation by amateurs of wines and liquors in vessels which contain lead alloys has caused some plumbism in the Unites States. Many years ago this was such a common cause of poisoning in the cider district of Devonshire that "Devonshire colic" became a well-known disease. In the sixteenth century "Colica Pictonum" was epidemic in France near Poitiers, and later this was found to be caused by the lead added to wine to prevent souring. On standing, wine thus treated could not turn to vinegar because the lead reacted to form lead acetate.

Other less frequent causes of plumbism are the drinking of rather acid

water in which lead pipe has been immersed; the use of hair dyes or cosmetics; the sucking of painted toys; and the ingestion of lead salts with suicidal intent or to cause abortion. The amount of lead which enters the organism need not be large to produce severe symptoms, as in a case of poisoning recently reported after the ingestion of 1.33 gm. of lead acetate (less than 750 mgm. of metallic lead).

It is now known that lead may be absorbed from the gastro-intestinal tract, from the respiratory tract, and even from the mucous membranes of the nose and mouth. The respiratory tract is the more dangerous path of entry, because, while a majority of the lead absorbed from the gastro-intestinal tract is caught by the liver and excreted, that absorbed by the respiratory tract enters at once into the circulation and is distributed throughout the organism. Subcutaneous or intramuscular deposits of lead enter the blood-stream so very slowly that intoxication from bullets, if it occurs at all, is very rare. Absorption of inorganic lead salts from the skin is probably negligible.

Lead is a cumulative poison because it is stored in relatively large amounts in the solid portion of the bones. Until it is liberated from the skeleton this deposit does no harm. During absorption, the blood-stream carries lead to all the organs, especially to the bones, liver, kidneys, and intestines. After active absorption has ceased almost all the lead in the body (more than 95 per cent.) is to be found in the bones, from which it is excreted extremely slowly. Symptoms of lead poisoning appear when lead is circulating throughout the organism as a result either of absorption from outside sources or of liberation from the deposit in the bones.

There are three possible paths for the excretion of lead from the body—the gastro-intestinal tract, the kidneys, and perhaps the skin. The larger part of lead eliminated is in the feces, but the fact must be kept in mind that during active absorption of lead the feces also contain some which has been ingested but has never been absorbed. The amounts of lead excreted in urine are usually very small; but even after exposure to lead has ceased this slow elimination (usually a fraction of a milligram per day) may continue for months, and even for years. Excretion from the skin is probably small and is not yet proved.

Morbid Anatomy.—Some claim that an abnormally high incidence of arteriosclerosis, chronic interstitial nephritis, gastric ulcer, and cirrhosis of the liver are found in lead workers. The male gonads are said to degenerate. Palsy usually follows a peripheral degenerative neuritis; and in permanent palsy many of the anterior horn-cells in the cord disappear. The affected muscles are atrophic and fatty, and the muscle tissue itself is gradually replaced by fibrous material. There are no other definite pathological changes.

Symptoms.—Acute Poisoning.—True acute poisoning is to be seen only after the sudden ingestion of large doses of lead. In animals the symptoms are vomiting and collapse, and there may be a peripheral destruction of large quantities of red blood-cells accompanied by acute anemia and sometimes by hemoglobinuria. The marked general weakness, loss of appetite, diarrhea, and dehydration may result in death or in a more chronic type of poisoning. In very susceptible individuals the onset may be rapid and intense after only slight exposure. This is frequently called acute lead poisoning, although the symptoms are those of the more chronic type.

Lead colic may develop after exposure of only a few days, and may be associated with constipation or sometimes with diarrhea. Severe acute anemia may occur, and very rarely, mild nervous disturbances.

Chronic Poisoning.—In chronic plumbism the patient usually suffers from great weakness and lassitude, obstinate constipation, and often from intense colic. A peculiar pasty appearance of the skin is quite characteristic of the condition. The several features peculiar to lead intoxication will here be considered individually.

(*a*) *Changes in the Blood.*—One of the earliest evidences of lead poisoning is a change in the nature and number of red cells in the circulating blood. A marked destruction of erythrocytes in the peripheral circulation is accompanied by increased production of red cells. The counterbalancing of the loss of red cells by stimulation of bone marrow activity maintains the cell count above 3.5 or 4 million cells per cubic millimeter so that anemia is usually not as severe as the pallor of the patient would indicate. Recent investigations of the mechanism of destruction of blood have shown that lead reacts with the inorganic phosphate to form insoluble lead phosphate and acid on the surface of the cells. This renders the cells inelastic and brittle, so that they are probably broken more easily than normal cells by the trauma suffered in circulation.

The most characteristic change in the blood is the appearance of "stippling," a punctate basophilic granulation in the cells which is best demonstrated by dilute Unna's alkaline methylene-blue stain. This appears during absorption and may continue for many months after absorption of lead has ceased. Stippled cells are probably degenerating young reticulated cells. Their presence in the blood is not absolutely pathognomonic of lead poisoning, as a few may be found in cases of pernicious anemia, leukemia, and sometimes even in normal blood; but such large numbers as 100 per million red cells do not appear in adults in any disease except lead intoxication. Stippling is, therefore, one of the reliable criteria for establishing the diagnosis of lead absorption.

(*b*) *The "Lead Line."*—The "lead line" on the gums is a second important sign of plumbism, and is very valuable in making a diagnosis. It is due to a deposit of lead sulphid about the blood-vessels in the tips of the papillæ, and therefore appears most plainly about pyorrheic gums. When examined with a lens it has a punctate appearance and is seen to lie a little below the margin of the gum. A piece of paper inserted between the gum and tooth distinguishes stippling from staining of the tooth root. The peculiar localization distinguishes this from the other pigmentations of the mouth which are more diffuse. The lead line is practically pathognomonic of lead absorption, but not of poisoning. It may persist for many months after exposure to lead has ceased. It must be distinguished only from the line produced by bismuth.

(*c*) *Colic.*—Abdominal colic is also a common early manifestation of lead intoxication, and occasionally occurs in susceptible people after only a slight exposure. It is usually preceded by constipation and indefinite abdominal pain. While the character of this colic in individual cases varies greatly, it is usually very intense and prolonged. The pain which is generally felt below the umbilicus is often relieved by pressure. During attacks the abdomen is scaphoid in shape, not tender to pressure, and, while resistant, shows no evidences of true abdominal muscle spasm. Probably

paroxysms of pain occur when peristaltic waves approach areas of marked tonic spasm in the intestines. This lead colic is often very difficult to differentiate from an acute abdominal inflammation; but diagnosis is aided usually by other signs of lead poisoning. It should also be remembered that in lead poisoning the white count is only slightly increased, if at all, that there is a relative lymphocytosis, and usually no fever. The intense pain in most cases stops within about a week after absorption of lead has ceased, but may be remittent for some time thereafter.

(*d*) *Palsy.*—Palsy has been recognized as one of the symptoms of lead poisoning for many years. Although in 1834 Tanquerel des Planches reported that it occurred in 10 per cent. of the 1200 cases he had examined, it is now relatively rare, because of improvements in industrial processes. A general weakness and tremor usually precede the actual onset of paralysis. This tremor, which is an early and relatively common symptom, is well demonstrated by extending and actively spreading the fingers. The paralysis which may follow is similar to peripheral neuritis and is usually rapid in onset and painless. One of its very striking characteristics is its early localization in the most used muscles of the arms: the extensors of the wrists and fingers of the right hand are first attacked in a startlingly specific manner producing the characteristic finger- and wrist-drop. Paralysis may also appear in the peroneal muscles of the legs and produce a steppage gait, and occasionally in the back and eyes. Optic neuritis is known to occur. After absorption of lead stops, function may be recovered within several weeks, but usually there is gradual improvement for many months. If exposure to the poison continues, paralysis may be permanent and progressive, and may simulate progressive muscular atrophy.

(*e*) *Psychosis.*—In many cases of lead poisoning there is mild mental depression, while occasionally transient delirium and convulsions or hysterical attacks occur. Rare cases show severe cerebral involvement characterized by marked delusions and mania leading to convulsions and death. This psychosis may closely simulate general paresis in its clinical manifestations, though the Wassermann reaction is not positive.

(*f*) *Gout.*—In England gout is frequently reported in chronic cases.

(*g*) *Degenerative Changes.*—That the late manifestations of lead poisoning are largely degenerative, and are caused by the continued action of the lead stream, is shown strikingly by the frequent appearance of arteriosclerosis, contracted kidneys, and a resulting high blood-pressure and hypertrophy of the heart.

Occasionally acute attacks of poisoning develop in workers long considered immune, or even in individuals no longer exposed to lead. These late developments do not differ from other acute manifestations of plumbism.

Diagnosis.—The diagnosis of lead poisoning is often difficult because evidence of absorption without signs of actual intoxication may frequently be observed. Usually, unless at least two symptoms characteristic of the poisoning appear, a definite diagnosis of plumbism should not be made. The best evidence of intoxication is marked stippling of the red cells; but lead line, colic, constipation, anemia, muscle weakness, and wrist-drop are also important. The excretion of lead in the urine and feces is also very significant. A majority of the lead excreted is to be found in the feces, but its presence is of little diagnostic value unless all possibility of swallowing

lead has been removed. Lead in the urine, however, always denotes that absorption has occurred. Excretion may continue long after exposure has ceased; it merely proves that lead has been absorbed by the organism, and is not in itself a proof of intoxication.

Final diagnosis depends upon all of these considerations, but usually requires at least two of the described features. Although in some cases both the lead line and slight stippling appear in workers without other evidences of poisoning, marked anemia, colic, or nervous lesions are usually deciding factors in diagnosis.

Lead poisoning often appears after prolonged exposure, but sometimes even after exposure has ceased. This tardy development of symptoms is probably caused by liberation of the lead deposit in the bones which occurs during severe illness, or alcoholic debauches. It has also been reported, rarely, after taking potassium iodid. Thus if lead is held harmlessly within the body some change in the general metabolism may precipitate an attack of poisoning. The disease should always be thought of in acute abdominal crises, as it is not infrequently the cause of unnecessary surgery.

Prognosis.—The prognosis depends upon the type of symptoms. Colic usually disappears within a few days with suitable treatment, while anemia, constipation, and general debility hang on for many weeks. Palsy disappears very slowly, and in some cases is permanent. Severe psychoses are often fatal, but they may become chronic, and in rare cases they disappear promptly and completely. The mild depression, which is so common a symptom, is lost as other acute symptoms subside.

Prophylaxis.—Dust and the contamination of food and tobacco are the most common sources of poisoning at the present time. If proper precautions are taken by workmen and employers to avoid all dust hazards by suitable ventilation, aided by the use of respirators, intoxication may be very largely prevented. The incidence of poisoning among painters may be greatly reduced by the use of sand-paper which can be moistened. Clean hands and clean places to eat must be insisted upon. The toxicity of lead varies so much with individuals that no definite prediction may be made as to the amount which will cause symptoms of poisoning to appear, although Legge states that a continued absorption of more than 2 mgm. per day may produce intoxication.

Treatment.—Relief of the severe colic of lead poisoning often demands much medical ingenuity. *Amyl nitrite* or *nitroglycerin* frequently brings prompt relief, also *atropin* in large doses or intravenous calcium chlorid. A hot-water bottle may be comforting. If diagnosis is certain, a saline *cathartic* or an *enema* is also desirable. *Morphin* is rarely necessary to relieve the pain.

After the subsidence of acute symptoms the purpose of the treatment is to gradually eliminate lead from the body. Since it was first recommended by Melsens in 1840, *potassium iodid* has been employed to increase the excretion of lead. Because it is said to precipitate occasionally acute symptoms, the initial doses should not exceed 1 gm. per day, and the amount should then gradually be increased.

Recently *a new method of treatment* has been developed which aims to liberate lead from the deposit in the bones (Aub and Minot). In acute cases a diet containing much calcium should be given. This consists of 2 quarts of milk and 3 gm. of calcium lactate daily, and tends to reduce the excretion

of lead. After disappearance of acute symptoms such a diet should be replaced by one containing as little calcium as possible. With this, large doses of phosphoric acid or of ammonium chlorid should be given to produce a negative calcium balance and thus tend to liberate lead from the bones.

Saline cathartics have long been recommended to relieve constipation. They probably do not increase the excretion of lead. Treatment for the *anemia* of lead poisoning should be like that for any secondary anemia. *Palsy* best responds to galvanic current and massage and should be treated like a peripheral neuritis. Disappearance of the acute symptoms of plumbism does not signify that the disease is cured. Treatment to stimulate elimination of lead and to regulate the bowels should be continued for a long time after the more distressing symptoms have been alleviated.

It is always desirable for a patient suffering from any of the symptoms of lead poisoning to avoid further exposure to lead.

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THE INTOXICATIONS

ALCOHOLISM

Overindulgence in intoxicants in youth is an endeavor to cast off restraint and enjoy emotions; overindulgence in intoxicants later in life, and in narcotics at all ages is the result of a disturbance in the psyche and personality. The so-called "physical thirst" and the "inherited desire" are not realities, but merely a manifestation of psychic restlessness due to unknown psychological causes. It is usually said that weakness of will permits an individual to drink to excess or to take opiates, but this "will" is merely the sum total of psychic energy expressed in voluntary action and coincides with the wishes and desires propelled by the emotions and instincts.

Acute Alcoholism.—Dipsomaniac or periodic alcoholism is usually referable to the entrance of unhappy and suppressed emotions into the consciousness at regular or irregular intervals with such intensity that they are intolerable. Periodic drinking, especially in women, is almost always a conscious or unconscious attempt to obtain forgetfulness. Unhappy love affairs, sorrow, disappointment, and everything that can produce bitterness may drive the patient to seek solace in drink. Unless the *psychic equilibrium* can be obtained, the excessive use of alcohol or some narcotic will continue. In some individuals *chronic tobacco poisoning*, particularly that caused by cigarette smoking, may lead to an alcoholic crisis. At first, the more such patients smoke the more they are quieted, but soon the excessive use of tobacco increases their nervousness, and as they are also hypersensitive to alcohol as well as to tobacco, when they attempt to reduce the nervousness which results from smoking by drinking, they lose their sobriety after a single drink and inevitably take an excess of alcohol. Still another type of periodic alcoholism is coming to be more generally recognized. This is due to *mild, recurrent, manic-depressive insanity*, and comes on irregularly as the result of worry, physical strain, and overwork. It differs from the other forms of periodic alcoholism in that the debauches are apt to begin with excessive sexual indulgence. The consequent drinking is merely an attempt to prolong the enjoyment of the manic ecstasy.

Symptoms.—The symptoms of acute alcoholism need hardly be described. The face is flushed, the pulse full and rapid, and the respirations deep and slow, occasionally stertorous. The pupils are dilated. The temperature is normal or slightly subnormal; sometimes after exposure to intense cold it may be as low as 90° F. The breath has a strong alcoholic odor. The speech is thickened, the judgment blunted, and the ability to appreciate the ordinary situations of daily life is lost. Curious and stupid mistakes result from the inhibition of judgment, memory, and intelligent control of the distorted emotions. Since the emotional balance of each individual is unique, the expression of acute drunkenness varies. Some patients are cheerful and generous, while others tend to be quarrelsome and ugly. In the early stages of the intoxication the motor activity is increased; in the late stages there is marked loss of muscular co-ordination and the gait becomes staggering. The presence of a certain quantity of alcohol in the blood makes the subject tend to fall into stupor and sleep.

Treatment.—When alcoholism is associated with excessive smoking, both tobacco and alcohol must be avoided. The real cure for the condition is, however, to discover the origin of the psychological dysequilibrium. The drinking in which patients with manic depressive insanity indulge is best cured in an institution. It is desirable not to commit the individual permanently until it has been ascertained whether or not he will recover promptly. Commitment is, however, necessary at times until the acute psychosis disappears.

Alcoholic Trance (*Automatism*).—The condition known as alcoholic trance develops in patients who have taken very little alcohol as well as in those who are chronic drinkers. It is really a dissociation of consciousness which brings complete forgetfulness. Individuals in this condition do not necessarily appear drunken, are not disturbed, and go about their daily tasks in a purely automatic fashion. They may wander off to some strange place quite unconsciously and not know how they arrived there or what they have done, when the realization of their surroundings returns several days later. During the period of automatism such individuals may commit a crime, murder, or theft. Although they may be arrested, and receive punishment, they never remember their misdeeds after consciousness returns. In some cases brilliant pieces of work have been performed in this automatic manner. The forgetfulness is real and often complete. Patients with this disturbance should be treated as though they were mentally incompetent and unable to differentiate between right and wrong, but this fact is difficult to impress on the average layman, and they are often punished by the courts for ordinary drunkenness.

Chronic Alcoholism.—Morbid Anatomy.—Chronic intoxication with ethyl alcohol causes degeneration of the parenchyma of the various viscera, chronic congestion, and proliferation of the connective tissue, which finally destroys and replaces the parenchymatous cells. The *heart* undergoes fatty infiltration and degeneration and the cardiac fibers themselves suffer brown atrophy and fibroid replacement. Excessive fatty degeneration of the myocardium is especially common in young female alcoholics. In the *aorta* there is often atheromatous change. Degeneration of the *peripheral blood-vessels* is not so common except in the vessels of the viscera. It is difficult to say how much this results from the action of the alcohol itself and how much from the infections to which alcoholics are susceptible. There is no characteristic change in the *lungs*, but the high incidence of pneumonia and tuberculosis indicates that the resistance to pulmonary infection is diminished. The most common *hepatic lesion* is a combination of cirrhosis and brown atrophy with fatty or parenchymatous degeneration. In the *spleen* there is chronic congestion and fibrosis. The *pancreas* frequently shows evidence of chronic fibrosis. In the *stomach* chronic atrophic gastritis is commonly associated with the hemorrhagic type. Although the mucosa of the *small intestines* in large measure escapes the direct action of alcohol, edema and congestion sometimes develop. The most common lesion in the *kidneys* is chronic parenchymatous nephritis, which is often accompanied by congestion, but chronic interstitial nephritis occurs almost as frequently. Acute nephritis is not common. The *gonads* undergo atrophy at an unusually early age.

Lesions of the *central nervous system* are not characteristic. The membranes of the brain are usually congested, and the quantity of fluid in the

pia-arachnoid space is abnormally large. This fluid replaces the tissue lost within the unyielding skull. Not uncommonly the cerebral tissue itself becomes edematous. Pachymeningitis occurs at times, and pachymeningitis hemorrhagica frequently, as the result of trauma to the diseased vessels. At autopsy examinations recent cerebral hemorrhages are often seen, and in some cases old encysted hemorrhages. *Alcoholic neuritis* rarely involves the peripheral nerves alone, but is usually associated with moderate degeneration of the cortical cells of the cerebrum, particularly in the motor areas, with degeneration of the descending fibers in the internal capsules and with degeneration in the descending column of the spinal cord. These lesions do not affect a single tract, but involve widely separated fibers. When the condition is severe the morbid changes can also be found in the ascending tracts of the cord.

Symptoms.—In the early stages of chronic alcoholism the most obvious symptoms are resentment of any suggestion of undue drinking, and the desire to deny such indulgence in spite of the realization that it occurs. This puts the individual on the defensive at home and renders him irritable and difficult to live with. The family are the first to notice the *change in character*—quick temper, unreasonableness, and lack of consideration for others. To the outside world the subject continues to be as cheerful and bright as usual, although he tends to take unreasonable offence on slight provocation. He may still be capable of responding to emotional appeals of the higher order, but an instability develops, and the desire to finish anything with persistent vigor is replaced by a tendency to stop readily. The continual defensive attitude causes untruthfulness, which often appears more serious than it really is because the patient observes incorrectly and is unable to pay attention to his environment. An alcoholic will make any promise to avoid annoyance, will give any excuse to stop discussion, and will do anything to dodge the responsibility of facing reality. It is much easier for him to live with blunted emotional values than to face the realities of life. Consequently he continues to drink.

The condition of chronic alcoholic narcotism finally falls into one of three classes: chronic cerebro-arteriosclerosis, paranoia, or general paresis. The manifestations of *cerebro-arteriosclerosis* are loss of memory, depletion of the emotional values, and increasing stupidity. A patient in this condition does not consume enough alcohol to cause fatal injury to the viscera, but continues to suffer progressive mental deterioration and is a nuisance to his family and to the community. The *paranoiac* is irritable and suspicious, full of self-righteousness, and is convinced that he is persecuted by his friends and family. He continually blames his short comings on ill-luck or on the injustice of others, in order to justify his continued drunkenness and neglect of all responsibility. A man in this condition is liable to accuse his wife of gross infidelity and wrongdoing of which he himself is guilty. The accusation of sexual misconduct of the husband or wife is characteristic of chronic alcoholism. The alcoholic paranoiac is a dangerous individual because any dislike or hatred is liable to express itself during intoxication in definite action and lead to some crime such as injuring or killing a member of the family. In the *paretic type* of chronic alcoholism there are delusions of grandeur, the memory is lost, and the judgment becomes characteristically false.

Prognosis.—The prognosis depends on the severity of the visceral and

cerebral lesions, and on the possibility of rendering the psychological equilibrium more nearly normal by the solution of the domestic, social, and personal problems of the patient.

Treatment.—It is not always possible to give an individual with chronic alcoholism the proper treatment at home. In many instances it is necessary to resort to institutional care in order to combine the requisite physical treatment with investigation of the psychological basis of the abnormality. This is particularly true of paranoiac patients who will not otherwise stop drinking. After such individuals have once been committed to an institution no attention must be paid to their pleadings, their threats of suicide, or revenge, nor to the ill-advised demands of their friends that they be given one more chance, for the only hope of recovery lies in forced abstention from alcohol. The best method of stopping the intoxication with alcohol is the belladonna treatment outlined for morphinism. This does not cure the patient, but is the most satisfactory and rapid means of restoring sobriety. The only possible chance of cure lies in the reorganization of his point of view and the restoration of normal psychic balance.

Conditions Associated with Chronic Alcoholism.—*Delirium tremens* is a type of acute insanity characterized by delirium with trembling and marked emotional excitement.

Incidence and *Etiology.*—Excessive indulgence in alcohol rarely brings on an attack in a temperate person; in the chronic alcoholic, delirium tremens may follow a temporary excess or develop subsequently to the sudden withdrawal of alcohol. While the cause of the condition is chronic alcoholism, some unknown factor seems to determine whether delirium tremens or acute alcoholic insanity is to result from the intoxication. The incidence is highest in individuals about forty years of age; it is low in those less than thirty years old. The condition is more common in northern climates where spirituous liquors are used than in warmer climates where wine and beer are the common beverages. *Trauma* may produce delirium tremens in men who have drunk large quantities of alcohol, and severe excitement or shock not infrequently produces it in individuals who have been accustomed to drink daily without becoming intoxicated. Fractures and injury to the respiratory apparatus are apt to induce the condition, but injuries are less liable to play an etiological rôle than are *infections* such as erysipelas and pneumonia.

Symptoms.—As a rule, delirium tremens does not set in suddenly, but is preceded by excitement, restlessness, peevishness, and insomnia. As the patient drops to sleep he is disturbed by dreams which produce a sense of fear or anxiety. There is frequently precordial oppression and pain. The patient may complain of ringing in the ears and dizziness. This incubation period varies in length from a few days to nearly two weeks. When the delirium is a complication of an infectious disease it usually appears on the third or fourth day, but in severe cases it may begin within forty-eight hours. When the delirium has once developed the patient appears seriously ill and has an anxious expression. The face is cyanotic or congested and covered with sweat. Individuals who are old or feeble appear pale and indifferent, and suffer from hallucinations connected with their daily work. The "menagerie" delirium concerning animals and monsters is not usual, although it is not uncommon. The delirium is very active as a rule, and the hallucinations are extremely vivid. Patients give the

impression of seeing tangible things and of reaching out to pick up objects which seem actually to exist. The muscular tremor renders their gait unsteady, and as they pay attention only to their delirium they often injure themselves without realizing it. The speech is either trembling or stuttering because of the muscular tremor, or the words are blurted out explosively.

In delirium tremens the most common hallucinations are visual; auditory disturbances are much less frequent, and those of taste and smell are rare. All types produce fear which varies somewhat in intensity according to the degree of poisoning. Patients retain their sense of self, but lose all idea of time. They do not know where they are, feel confused about their relation to the outside world, and have a disconnected memory, although they are quite clear about their occupation, their previous mode of life, and their personality. There is great susceptibility to suggestion which is related to the hallucination. The attention may be obtained momentarily, but is held with great difficulty if at all. The delirium lasts between two and ten days (average five days). The sleeplessness which persists throughout this period is followed by *deep sleep* which continues without interruption for twelve to thirty hours. This leaves the patient sensible, free from hallucinations, and correctly oriented, although the mentality is reduced. There is never complete remembrance of the illness in spite of the fact that the essential details can be recalled.

The physical manifestations of delirium tremens vary somewhat with the age of the patient. In young, vigorous individuals the *pulse* is full and bounding, while in the feeble and elderly it is frequent and weak. The *tongue* is coated or glazed. The *temperature* remains normal when there is no excessive muscular activity unless a complication has set in; but it may rise with great muscular exertion to 101° F. or even in a few cases to 104° F. In extremely hot weather patients can readily bring on a fatal heat stroke in which the temperature rises to 108° to 109° F. There is no characteristic change in the *blood*, although the polymorphonuclear leukocyte count is said to be raised and the mononuclear count lowered, but without leukocytosis. In severe delirium eosinophilic cells are absent. The *urine* at times contains a small quantity of albumin. *Lumbar puncture* does not reveal any typical changes.

Diagnosis.—Delirium tremens can usually be recognized by the typical tremor, the furring of the tongue, the normal temperature, the active or muttering delirium, and the disorientation. The hallucinations are usually concerned with the daily occupation: hypochondriac delusions of sensations in the stomach and viscera occur only as evidence of other mental diseases.

Prognosis.—Frequently under treatment true delirium tremens does not develop beyond the preliminary stage, and suitable therapy, sleep, and rest stop the attack. The more intense the delirium, the restlessness, and the consequent exhaustion, the more serious is the prognosis. Uncomplicated delirium tremens proves fatal in about 15 per cent. of cases. If it is associated with such infectious diseases as pneumonia the outcome is apt to be fatal. The delirium tremens which follows trauma proves fatal in about 50 per cent. of patients.

Treatment.—There is *no specific treatment* for delirium tremens. It is essential to produce sleep, stimulate the nervous system and circulation during the withdrawal of alcohol, and feed the patient. *Sleep* may be obtained by the administration of hypnotics. If these or any other

medicines are given orally, the stomach must be stimulated by 5 to 10 drops of tincture of capsicum and 10 to 15 drops of tincture of ginger to prevent stagnation of the gastric contents and consequent injurious absorption of several doses at one time. It is common to give 2 to 3 drachms of paraldehyd or 20 to 30 grains of chloral (with or without 1 to 2 grains of codein by mouth) in a single dose. This is often combined with 10 to 20 minims of tincture of hyocyamus. It must be remembered that the paraldehyd itself produces delirium in a small number of individuals. Morphin must be avoided as far as possible, as it increases the cerebral congestion and may lead to the morphin habit. Apomorphin (1/10 grain) given hypodermically with strychnin (1/30 grain) is necessary at times to quiet a wild delirium and induce relaxation and sleep. Veronal or any barbituric acid, while effective in producing sleep, perverts the personality and usually renders the patient unreasonable and hard to manage after he has wakened. The marked tremor is best controlled by administration of strychnin and ergot; or, in some cases, by giving nux vomica ($\frac{1}{2}$ grain), ergot ($\frac{1}{2}$ grain), and extract of gentian every two hours. All alcoholic patients should be thoroughly purged at the beginning of any form of treatment with 2 or 3 compound cathartic pills followed by salines, or by other effective cathartics. Restraint should not be employed unless it is essential. In case of need, however, a sheet may be passed behind the neck, over the shoulders, under the arms, and back to the head of the bed, and the feet tied with another sheet. This is more satisfactory than the old-fashioned canvas jacket.

Alcohol may be withdrawn gradually in elderly patients during the first thirty hours of treatment, but in young, vigorous patients it is usually best to cut it off immediately. It is wise to administer as much as 1 or 2 ounces at intervals during this tapering-off process. Smaller quantities are tantalizing and ineffective.

Since many alcoholics live for a long time on alcohol alone *without food* they are subject to intense gastritis. This should be immediately treated by active catharsis to empty the colon, and by administration of milk or some other easily digested food. If food or medicine cannot be retained, a teaspoonful (60–80 grains) of soda bicarbonate in an ounce of peptonized or plain milk should be given every hour to allay the gastritis. Patients who cannot retain even this may receive 20 grains of cerium oxalate and $\frac{1}{4}$ to $\frac{1}{2}$ grain of codein with the first few doses. At times this is not effective, and 5 grains of Tulley's powder may be added to the bicarbonate of soda.

Acute Alcoholic Hallucinosis.—In acute alcoholic hallucinosis the *hallucinations are chiefly auditory.* Patients seem to hear familiar people speaking to them and about them vividly and clearly, and are apt to hear abuse hurled at them from every stranger on the street. They often feel that they are being pursued and will be harmed, or that someone is waiting outside the door to injure them. This sometimes renders patients dangerous, for they blockade themselves in their rooms with firearms which they do not hesitate to use. Such patients are driven by their own fear and sense of persecution to commit suicide or to appeal to the police for protection. Visual hallucinations are sometimes associated with the auditory. The tremor and physical appearance characteristic of delirium tremens may develop with this acute alcoholic insanity. In the early stages of the condition patients are restless and sleepless, have an intense

dread, are particularly sensitive to ordinary noise, and are disturbed by dreams. Unlike subjects of delirium tremens they may have slight hallucinations referable to the viscera. These patients are very suspicious and misinterpret all therapeutic measures. The sense of orientation seems to be retained except when the condition approaches the border line of delirium tremens. Symptoms of neuritis are common.

Diagnosis.—Hallucinations of hearing and a strong suicidal tendency are characteristic of acute alcoholic insanity, and are a means of distinguishing the condition from delirium tremens. In some cases, however, when the symptoms of delirium tremens develop in one attack and those of alcoholic hallucinosis in the next it is very difficult to be sure of the diagnosis.

Prognosis.—This psychosis lasts between six days and two months: it rarely continues longer than this. As the patient improves he is free from hallucinations at intervals and has a keen insight into his condition. This realization sometimes comes so rapidly that patients recognize the nature of their hallucinations before they have completely disappeared.

Acute delirium may develop into chronic delirium or Korsakoff's psychosis. The prognosis is good, however, if the patient is put into an institution and properly cared for. The more nearly the condition resembles delirium tremens the shorter its duration. The more pronounced the ideas of grandeur the longer it lasts. Permanent insanity is liable to result from continued indulgence in alcohol if the delusions are systematized. The susceptibility to intercurrent disease is less than in delirium tremens.

Treatment.—Patients with acute alcoholic hallucinosis should be treated as acutely insane, kept in bed, given hypnotics, and made to sleep. Otherwise, they require the treatment outlined for delirium tremens. Special care is necessary to prevent suicide. After recovery the psyche is more easily restored to normal than after delirium tremens.

Korsakoff's psychosis is chronic alcoholic delirium with polyneuritis. It affects women more often than men, and usually develops during the prime of life. The *cause* in most cases is long-continued indulgence in alcohol.

Morbid Anatomy.—The lesions are those of peripheral neuritis, as well as changes in the meninges and in the cells of the cortex. The small hemorrhages of delirium tremens and the visceral abnormalities associated with chronic alcoholism may also be present.

Symptoms.—In the prodromal period there may be irritability, mental aberration, restlessness, or stupor. The psychosis usually begins, however, with acute delirium, which is often indistinguishable from delirium tremens or acute alcoholic hallucinosis. Hallucinations are more common during the early stages of the delirium. They are chiefly those of touch and sight, and occur most frequently at night. The *mental manifestations* are a definite disturbance of attention, marked loss of orientation, especially as to time, and loss of memory for recent and sometimes for past events. Some patients retain islands of memory. To compensate for the loss of memory, confabulation, which consists of delusions and imaginary experiences, is common. There is great susceptibility to suggestion. In different patients the *emotional stability* varies greatly, some are excited, some overelated as in paresis, some melancholic, anxious, and disturbed. Toward the end of the disease they become very irritable and indifferent, or silly and childish. There is a noticeable lack of mental initiative.

The *neuritic symptoms* are unstable gait, walking with the feet far apart, weakness in the knees, muscular relaxation, and sensitiveness to the touch. The legs are more affected than the arms. Paralysis of the extensors is more common than that of the flexors, but in some patients the muscles are irregularly affected. Marked paralysis leads to atrophy. Disturbances in the sense of position and in the senses themselves are common; a delayed reaction to pain and ataxia of the upper extremities occur frequently. Even the cranial nerves may be affected. The sense of smell is retained, but the optic nerves may become neuritic. The pupils may be normal, but are frequently uneven and react slowly. The typical Argyll-Robertson pupil is found in some patients, and in others a nystagmus-like twitching not infrequently develops during the last stage, with ptosis. Abducens paralysis is not uncommon. Difficulties in speech may develop. The pneumogastric nerves are often affected. The *pulse* may be rapid or fall to 38 or less.

Prognosis.—The disease is often protracted. After the acute delirium has passed a chronic stupor may develop, which leads to death within two or three weeks; or general apathy and increasing weakness which prove fatal after three or four months. The chronic disturbances of the liver and kidney which are associated with chronic alcoholism frequently cause death. If recovery takes place, the neuritis usually improves before the mental disturbances. Neuritic symptoms may completely disappear, or lead to permanent atrophy and paralysis. Mental improvement is usually slow; the power of retention returns before orientation. Even when the intellect appears to have returned to normal the finer emotional values seem to have been burnt out.

The prognosis is doubtful in all recent cases. The more severe the delirium, the more unfavorable the outlook. Involvement of the cranial nerves and vagus is an unfavorable sign.

Treatment.—The delirium requires the same therapy as other types of alcoholic delirium, and the polyneuritis the same treatment as ordinary neuritis. For the undue intestinal putrefaction hydrochloric acid and nux vomica should be given, and the gastric digestion stimulated by administration of buttermilk. The intestinal tract may be disinfected with small doses of salol (5 grains every four hours) and castor oil (5 minims every four hours). When the skin is dry, iodin and arsenic should be injected (as cacodylate of soda) during convalescence. As the patient improves he should live outdoors and perform stated tasks to stimulate the mind.

Wet Brain.—This is a form of serous transudation which develops in chronic alcoholism after acute or chronic delirium and in all types of exhaustion. The condition occurs in both men and women. It most often develops after delirium tremens, but may follow injury or debauch without delirium.

Morbid Anatomy.—There is no inflammation. The excess fluid in the pia-arachnoid space is a transudate.

Symptoms.—The postdelirious stupor seems to be an exhaustion psychosis rather than the result of increased intercranial pressure or edema of the brain or meninges. If the condition follows several days of active delirium, the low mutterings associated with the semicoma, the facial flush, and the muscular trembling give way to a mask-like facies and great pallor. The patient usually lies flat on the back, with the legs extended, the head thrown slightly back, the half-opened eyes turned to the ceiling,

and the hands moving slowly in the motions of rope-climbing. The slow tremor of cerebral irritation is visible in the hands which are incessantly active. In the mumbling delirium and muttering, pronounciation of the labials seems impossible. Although the patient can be made to take food, there is a tendency for it to run into the larynx. This may cause pneumonia. The temperature is normal or slightly elevated; if it reaches 101° F. pneumonia is developing. The skin is hyperesthetic. Pressure on the arms and legs or about the abdomen is evidently painful. After this general condition has persisted for days or weeks, there may be slow improvement, or the coma may deepen so that the patient cannot be aroused. The arms and legs then become stiff, the reflexes exaggerated, and the neck stiff and slightly retracted. The muscles are hyperesthetic and the abdomen retracted. The eyes are closed, and the pupils are contracted and react slowly if at all. The active rope climbing ceases and the patient lies immobile. The tongue is dry and brown. Neither urine nor feces can be retained. The pulse is fast and feeble, and the extremities are cold. If death does not ensue within a short while, recovery is so slow that convalescence does not really begin for three or four weeks. In young patients, however, it may occasionally be sudden and rapid.

Prognosis.—Of the 15 per cent. of delirious patients who develop this condition, about 61 per cent. die. If the neck does not become stiff, the prognosis is good (unless pneumonia develops). If it does become stiff, the outlook is extremely bad.

Treatment.—As soon as even a suggestion of the condition develops, strychnin (1/30 grain) and ergot (30 minims) should be injected hypodermically every two hours. Caffein and camphor are also beneficial. Food is to be given at intervals, and thorough purging is desirable. As alcohol aggravates the condition, it must be avoided.

During convalescence such stomachics as nux vomica and ginger in small doses, or tincture of cinchona (2 to 3 drops) are excellent. These patients are very easily exhausted and should not be pushed during convalescence.

METHYL ALCOHOL POISONING

The symptoms of methyl alcohol poisoning are quite different from those of ethyl alcohol poisoning. They vary greatly with the severity of the intoxication and also with the personal idiosyncrasy of the patient. Some individuals are severely poisoned by very small quantities, while others are remarkably little affected by large amounts. The intensity of the poisoning is much increased if the methyl alcohol is consumed, even in small quantities, on consecutive days. *Mild intoxication* with methyl alcohol produces forgetfulness and mental haziness due to lack of complete consciousness. The sight may suffer permanent injury.

Somewhat *more severe poisoning* is evidenced by dizziness, nausea, vomiting, and constipation, or in rare cases by diarrhea. Whenever two or three compound cathartic pills do not produce catharsis in an intoxicated person, methyl alcohol poisoning should be suspected. Castor oil alone is effective in combating this constipation. Many patients complain of abdominal pain. Even this moderate poisoning is liable to produce sudden dyspnea and cyanosis which may come on without warning and prove fatal. Increasing amounts of formic acid may be passed in the urine for four or five days,

because the methyl alcohol is not broken down rapidly or continuously in the body. The sudden attacks of dyspnea may cause death at any time within the first six or eight days. Even when the patient seems to be comparatively well he is liable to die suddenly; although at times when the intoxication seems hopelessly severe, improvement begins without apparent cause. The *dyspnea* is intense both subjectively and objectively. The deep breathing does not provide the necessary air and does not change the cyanosis. This breathlessness is associated with *intense thirst.* Frequently the *pupils* suddenly cease to react and nearly complete blindness ensues; in some instances the accommodation may be merely weakened and not entirely lost. After this moderately severe poisoning dimness of vision and increasing blindness is the rule.

In the *most severe poisoning* the patient rapidly becomes comatose and seldom recovers. In the rare instances in which recovery does take place, total bilateral blindness is permanent. The partial restoration of sight which may follow methyl alcohol poisoning is completely lost after days or weeks, and the optic nerve atrophies.

Prognosis.—The prognosis is most uncertain. The vision rarely remains uninjured even in cases of moderate intoxication.

Treatment.—It is wise to keep the patient quiet and to induce thorough purging with castor oil. Sometimes intravenous injections of a 5 per cent. solution of sodium bicarbonate relieve the dyspnea. This alkali does not, however, always completely neutralize the decomposition products of methyl alcohol. Injections should not be too frequent, and the dose should be carefully adjusted. It is better to prepare the solution by adding sodium bicarbonate to sterile water than to sterilize the finished solution, for this is apt to change the bicarbonate into the carbonate.

No treatment of the optic nerve is very satisfactory. Administration of pilocarpin and sweat baths in the early stages, and hypodermic injections of strychnin seem to limit the extent of the secondary atrophy.

ALEXANDER LAMBERT.

COCAINISM

Cocain is not a narcotic, but a stimulant which relieves exhaustion and depression. It is often taken by alcohol and morphin addicts when the effect of the other drug wears off. Cocain is used as snuff in the form of a powder or injected hypodermically. When mixed with other drugs its effects are added to those of the other substances. The most injurious combination is heroin and cocain, for the obliteration of restraining impulses is then associated with ideas of persecution and with abnormally rapid reflex activity. These two drugs produce the most rapid degeneration of personality.

Symptoms.—Cocain relieves fatigue, inflates the personality, produces a sense of great muscular and mental strength, and makes its subject feel

that he can accomplish whatever he desires to do. The patient takes particular pleasure in the heightened sensitivity. His voluble conversation is without point, and his endless fault-finding letters are indirect even in their accusations. In addition to these strictly subjective effects cocain produces insomnia, muscular restlessness, and spasmodic movements similar to those of chorea major. The sense of persecution often leads cocain addicts to carry arms which they do not hesitate to use. This renders them very dangerous because they believe the hallucinations are a reality, and all reactions are abnormally quick. In the early stages of addiction patients become irritable, excitable, as the effect of the drug wears off, suspicious and morose, and suffer from insomnia and a feeling of anxiety and dread. Later stupor and restlessness alternate, and there is anemia, flaccidity of the skin, emaciation, and weariness. Auditory hallucinations are marked and hallucinations of sight are not uncommon. A peculiar sensation of something alive crawling under the skin, particularly in the palms of the hands, is often experienced. Smell, sight, and hearing are impaired. There is increased sexual excitement and diminished sexual power.

Insanity.—The insanity of cocain poisoning is similar to acute alcoholic insanity. The auditory and visual hallucinations which begin suddenly have quite a definite character. The patient believes that he is being threatened, that his thoughts are being secretly read, and that he is spied on through holes in the ceiling. The visual hallucinations are totally unrelated to previous occupation; black spots are often seen on a light ground and mistaken for insects. The crawling sensation under the skin is interpreted as injury by electricity. Cocainism is apt to produce delusions of infidelity and render its victim obscene. This type of insanity may develop rapidly and run its course within a few weeks. Although the acute hallucinosis disappears quickly after withdrawal of the drug, delusions may persist for weeks and months.

Diagnosis.—It is very difficult in the early stages of cocainism to determine whether or not an individual has the cocain habit. Rapid changes from exhilaration and untiring activity to restlessness, dulness, and depression should, however, arouse suspicion. Typically, the evidences of cocainism are early deterioration of judgment and ethical sense, increased recklessness and aimlessness, and a tendency to loquacity. The sensation of objects crawling under the skin is characteristic of cocainism. Sustained application is impossible.

A cocainist differs from most alcoholic addicts in that he seeks solitude for his indulgence and is more prone to turn his fancied injuries into resentful action. The delusions of persecution develop earlier than in alcoholism.

Prognosis.—The cocain habit is more readily broken than the morphin habit, because cocain is taken as an intoxicant and not to obscure the realities of life; but the danger of recurrence is always great on account of the vivid remembrance of the sense of power and success.

Treatment.—The treatment is similar to that for alcoholism or morphinism except that the drug is withdrawn immediately and not gradually. The belladonna therapy outlined for morphinism is excellent. Patients should be given strychnin and digitalis every four hours. For the first forty-eight hours of treatment they sleep almost continuously. If morphin or heroin has been used with the cocain, active delirium may develop sud-

denly at the end of this period. It responds very slightly to hypnotics. When it is over the patient usually says that he has slept quietly and has passed an excellent night. No recollection of the delirium remains. After the acute symptoms of cocain-need have passed it is essential to build up the patient physically and to solve the problems which impelled him to take the drug.

ALEXANDER LAMBERT.

THE OPIUM HABIT

(*Morphinism and Heroinism*)

Indulgence in the opiates depends on the same psychic need as alcoholism, except when continuous, legitimate, medicinal use for the relief of pain has produced an addiction. Heroin, morphin, and codein, unlike alcohol, produce no organic lesions, but merely poison the nervous tissue without demonstrable lesion. Of these three substances, morphin is the most effective analgesic. Heroin in its emotional narcotism is three times as strong as morphin, which, in turn, is eight times as strong as codein.

Heroin is employed in cough mixtures to allay pain. As a narcotic it is freely taken as snuff, or eaten, or injected hypodermically. In the early stages of poisoning it gives a sense of exhilaration and inflation of the ego. It destroys, more than all other narcotics, the emotional values, paralyzes all sense of remorse or responsibility to others, and obliterates the restrictions built up by social custom. Consequently, its victim becomes an antisocial, unmoral, self-centered savage, who without hesitation breaks any law and commits any crime. Heroin seems to be the favorite drug of the youth of the underworld. It intensifies any pre-existing lack of psychological balance, and drives its user to prey on his environment with a reckless, remorseless desire. A few individuals form the heroin habit by using the drug for asthma, certain chronic coughs, and bronchitis, but most addicts are youthful and begin to take heroin through curiosity or deliberately for inflation of their ego and obliteration of emotions.

Morphin is used to bring forgetfulness of the sorrows, memories, and tragedies of the world, and is, therefore, most commonly employed by people older than the heroin addicts. Quite frequently patients who suffer continuous pain have formed the morphin habit unwillingly; they differ from the "psychological addicts" in that they are eager to be free from the drug, and when once freed rarely touch it again unless renewed pain and suffering force them to it.

Codein is rarely employed except as a medicine, for it does not produce so persistent a reaction as heroin or morphin, and must, therefore, be taken more frequently. It is very useful as an analgesic or hypnotic, and is unlikely to produce a narcotic habit.

Symptoms.—The morphin habit is usually acquired insidiously, as the result of taking $\frac{1}{8}$- or $\frac{1}{4}$-grain doses several times a day for two or three weeks to allay pain, worry, unhappiness, or sorrow, or single nightly doses for insomnia. The discomfort of stopping this medication is so disagreeable

that patients make themselves believe that it is safe to continue it until they feel better. Few people can, however, take small doses of morphin consecutively for so long without running the risk of forming a habit, even when the drug is necessary as an analgesic. Physicians have but little appreciation of this fact.

The first signs of addiction are selfishness, indifference to small family matters, carelessness in dress, and a change in personality. Addicts are irritable and touchy on small excuse. The nausea is only a temporary manifestation.. As soon as large doses of morphin are used, forgetfulness becomes marked and the indifference to responsibility more noticeable. The *amnesia* of morphinism is similar to that of early senile dementia: names are forgotten first and recent events make little impression, although the memories of early life are retained. The power of *initiative* diminishes, and patients often remain in bed for days without sleep or stupor because they lack sufficient initiative to force themselves to move. There is marked psychic asthenia, a strong sense of inferiority, and a grumbling discontent which is a defense reaction to excuse the acts of the patient, and to attribute the cause of his unhappiness to others. Some addicts, particularly the psychologically unbalanced, are resentful and ugly in their self-defense, because they attempt to attain equilibrium by smothering the sense of inferiority. The analgesic addict, on the other hand, is filled with remorse and bitterly unhappy because of the stigma placed on him by society. Any criticism is bitterly resented. The lies told about the habit are a defense against the stigma. Such patients are not untruthful in other ways.

When the habit is well established the victim sleeps badly and suffers from nocturnal delusions which are often terrifying. These hallucinations are usually visual, but may be auditory; they very rarely involve the taste and smell. Some addicts cannot focus their eyes, although ophthalmoscopic examination reveals no organic cause for this inability. The *reflexes* vary; knee-jerks may be absent, but return after the habit stops. There is great range of *general sensibility;* paresthesia is common, and sometimes there are intense neuritic pains. The soles of the feet may become so hyperesthetic that the patient is forced to take short, jumpy steps. Chronic morphinism is apt to cause *constipation*, or alternating constipation and diarrhea. The *teeth* often undergo progressive caries. The *pulse* is slow and of low tension. *Cardiac action* is diminished. *Respiration* is usually shallow, and may be slow. Dyspnea on slight exertion is common.

Although most women are rendered *sterile* by the use of morphin, conception may take place despite the cessation of menstruation. Miscarriages occur frequently among addicts, but it is possible for pregnancy to go on to term. The children of morphin-taking mothers may be normal, but in some cases become acutely cyanotic twelve to twenty-four hours after birth, are restless, cannot be stilled, and die unless they are given small doses of laudanum or an opiate. Such infants can be freed from the need of a narcotic, and seem thereafter to be normal.

The Symptoms of Deprivation.—The symptoms which develop when *morphin* is taken away from an addict are restlessness, malaise, yawning, watering of the eyes, with a dull, drawn facial expression, and muscular trembling. Nausea, vomiting, and diarrhea frequently occur, as well as intense abdominal pain and a painful sensation of burning and tearing in the

muscles and joints. Patients in this condition will do anything to obtain their drug. They use cajolery, bribery, commit any crime, steal, or prostitute themselves to get the opiate. In some cases they become maniacal and attack their attendants. If cocain has been taken with the morphin, delusions of sight and hearing are liable to develop, or maniacal delirium. Without relief some patients die in collapse. The withdrawal of heroin does not evoke such prolonged symptoms as does the withdrawal of morphin, and collapse is less intense and frequent.

Diagnosis.—If the nutrition is normal and the pupils are not markedly contracted, there is no way of determining whether or not an individual is taking small doses of morphin except by complete isolation for forty-eight hours. The subject to be tested should be put in a hospital room after all his own clothing has been removed and every possible opening in the body has been searched for morphin. Careful observation is then necessary to prevent contact with the outside world.

Prognosis.—Braunlich believes that after hyoscin treatment, the only hope of permanent cure lies in inability to obtain drugs, for a man who has once been an addict is liable to suffer relapse even after years. He admits, however, that "proper treatment covering a protracted length of time will result in more cures than slip-shod stereotyped methods." The belladonna treatment when properly given obliterates the desire to take morphin.

Treatment.—The customary dose of morphin can be cut in half in twenty-four hours without the knowledge of the patient; and in the following twenty-four hours this reduced dose may, in turn, be halved; but after a certain reduction the critical point is reached at which lack of even a fraction of a grain produces marked symptoms. For this actual physical craving it is necessary to resort to either the hyoscin or the belladonna or other effective treatment.

Hyoscin Treatment.—The patient is undressed in an examination room, taken to a second room for a thorough cleansing, and dressed in hospital clothing in a third room. This prevents the hiding of drugs in the clothing or on the body. If heroin is the drug which has been taken, it is completely withdrawn. Five or 6 grains of morphin are administered in the first twenty-four hours, a dosage which is gradually reduced by the fifth day to 1.5 to 3 grains daily. On the fourth and sixth days a cathartic is given at 3, 6, and 9 o'clock to hasten elimination. This consists of 2.5 grains of calomel, 2.5 grains of powdered rhubarb, 0.5 grain of powdered ipecac, 1/180 grain of atropin sulphate, and 1/30 grain of strychnin sulphate. On the seventh day the patient receives a large dose of castor oil and 0.5 grain of morphin, the last dose of the drug. He is then put into the hyoscin ward, and when discomfort develops because of lack of morphin, hyoscin (1/200 grain) is injected hypodermically at sufficiently short intervals to produce an anesthesia comparable to the first stage of ether narcosis. This is continued for thirty-six hours. If the patient becomes agitated, or maniacal, 0.25 grain of morphin must be given. As the symptoms of withdrawal of an opiate do not ordinarily persist for more than seventy-two hours, the hyoscin administered during the first day and a half is usually sufficient. If, however, the patient suffers intensely or vomits severely, a few more doses of hyoscin may be given.

About ten days after admission the patient is placed in the convalescent ward. As the craving for drugs is most intense at this stage because of

sleeplessness and muscular weakness, very careful watching is necessary. Bromids and chloral are administered during this period, and if the pulse is weak, spartein sulphate and strychnin, occasionally with apomorphin (1/40 grain). After a week in the convalescent ward the patient may live in a dormitory, be given occupation, and receive no further medication except such as is necessary for intercurrent disease.

The *diet* varies with the stage of treatment. Before the hyoscin is given it is normal; during hyoscin administration only water may be taken; thereafter a regular diet is permissible as soon as it can be borne.

Belladonna Treatment.—On the evening before the beginning of the treatment the patient is given 3 to 5 compound cathartic pills and, if very constipated, 5 grains of blue mass. Six hours later these are followed by a saline. When the bowels have acted thoroughly two or three times the patient is given, in three divided doses at half-hour intervals, two-thirds or three-fourths of the total daily twenty-four-hour dose of morphin or heroin to which he has been accustomed. The larger amount of the drug is better if the patient can take this amount. One should observe the effects carefully, however, after the second dose, as the amount then equals four-ninths or one-half of the total twenty-four-hour dose. Some patients cannot comfortably take more than this at one time. With the last dose of morphin the patient receives in a capsule 6 drops (from a glass dropper, *not* minims) of the belladonna mixture which consists of a 15 per cent. tincture of belladonna and 1 part each of the fluidextract of hyocyamus and xanthoxylum. The belladonna mixture is now administered every hour. For the first six hours each dose is 6 drops; thereafter it is increased by 2 drops. Ten hours after the first dose of morphin, cathartics are given, and six hours later a saline, Rochelle salts, magnesium sulphate, citrate of magnesia, or sodium phosphate. The need for catharsis is distinctly greater than in alcoholism. Frequently 5 compound cathartic pills with 5 grains of blue mass are necessary. If the patient cannot take mercury, vegetable cathartic pills may be used.

As soon as the bowels have been thoroughly evacuated, half of the original therapeutic dose of morphin is injected. Administration of belladonna is continued and the dose is increased 2 drops every six hours. Catharsis, medication with saline, and injection of morphin are repeated after an interval of ten hours. This third dose of the drug is half the second. About the time that this is due patients not infrequently become nervous and feel the need of morphin. Codein is injected hypodermically for these symptoms, or a sterile solution of magnesium sulphate and codein mixed. The effect of 5 c.c. of a 15 or 20 per cent. solution of sterile magnesium sulphate is good.

The administration of belladonna is continued unless toxic symptoms develop. If such symptoms as dryness of the throat, rash, or marked dilatation of the pupils develop, medication must be stopped for several hours. When treatment begins again, it is necessary to reduce the dose to half the amount last given. To this quantity 2 drops may be added every hour. Patients are more comfortable when the physiological effect of the belladonna is maximal, but not toxic. The quantity needed to produce this effect varies greatly with different individuals: in some, 2 to 4 or 6 drops an hour suffice, while in others, 15 or 18 drops must be given hourly for several hours.

Between sixteen and eighteen hours after the third dose of morphin a fourth dose is given. This is half the third. With the magnesium sulphate and codein very little else is needed.

If the patient cannot sleep, codein (1 to 2 grains) and chloral (20 grains) may be given by mouth. At no time should there be nausea or vomiting. These symptoms yield to sodium bicarbonate or oxalate of cerium (10 to 20 grains every hour for four or five doses).

Seventy-two hours after the beginning of treatment the symptoms of morphin-lack diminish markedly and much less codein is needed. Less magnesium sulphate and belladonna is also required, but the administration of belladonna is continued to the eighty-sixth or ninetieth dose. Thereafter, if the patient is relaxed, and the stools are bilious green, a dose of castor oil may be given as the last step in medication. No codein or morphin may be taken after this, for there is danger of renewing the craving for drugs, which should have ceased completely at this stage. Insomnia is a troublesome and persistent symptom after gradual withdrawal treatment without medication or after the hyoscin or belladonna treatment. Baths and graduated physical exercise are the best remedies. There is danger that any hypnotic will form a habit at this time because of the desire to obliterate memories. For several days after treatment for narcotics, overeating or the eating of indigestible food will induce the appearance of withdrawal symptoms; these are easily relieved by enemata or cathartics. Any drug treatment for narcotism is merely the physical "unpoisoning" of the patient. The reconstruction of his psychological distortions is the only successful "cure."

ALEXANDER LAMBERT.

FOOD POISONING

Food may be harmful for various reasons. It may be in itself good and wholesome, but prove injurious to the individual because of bad dietetic habits, derangement of function, or lack of certain necessary constituents which give rise to deficiency diseases. Some individuals are hypersusceptible to certain articles of diet. Some plants and animal tissues normally contain toxic substances (ergot in rye), while others break down to form poisons, or become contaminated either accidentally or by intent. There are two well-recognized causes of food poisoning: (1) food infection caused by *Bacillus enteritidis*, or a closely allied micro-organism; (2) a toxin preformed in the food by the *Bacillus botulinus*. Other bacteria may produce injurious substances in food, but none which have been demonstrated to be poisonous by the mouth.

"Food poisoning" is acute illness due to some injurious substance in food or drink. The term is not suitable, for many attacks are caused not by poisoning, but by infection; many are derangements of function produced in a great variety of ways. The term "food poisoning," however, is much better than "ptomain poisoning," which is unscientific, misleading, and

incorrect. Mistakes in diagnosis are exceedingly common and can be avoided only by careful epidemiological studies and a thorough knowledge of the subject.

Various classifications have been attempted; none are satisfactory except those based on etiology. The commonest mistake is to classify food poisoning according to the type of food responsible: meat poisoning, cheese poisoning, potato poisoning, milk poisoning, etc. As a matter of fact, food infection is the same disease whether the bacteria are conveyed in milk, meat, potatoes, or salad. Botulism, or food intoxication, is the same whether it comes from sausage, ham, spinach, cheese, or olives.

Food that is prepared or preserved in some way is usually responsible for the disturbance. There is small danger in fresh food, little in cooked food, and none in sterile food. The chief sources of trouble are meat and milk, especially chopped meat, sausage, salads, brawn and milk products that are handled, prepared, or preserved. Food that is prepared hours before it is eaten constitutes an excellent medium for the growth of bacteria, especially in the summer.

The number of persons involved in outbreaks of food poisoning varies from one to several hundred, and is usually limited to the members of one or two families or to the participants of a meal or banquet. The more widespread outbreaks are almost all caused by infected milk. At Newcastle-on-Tyne, in 1912, 523 persons were affected by milk containing *Bacillus enteritidis*.

The fact that acute attacks of gastro-enteric symptoms are not necessarily due to harmful foods is commonly overlooked. Nausea, vomiting, cramps, and diarrhea may be due to indigestion, indiscretions in diet, eating when fatigued, or to exposure. The gastro-intestinal tract is exceedingly sensitive to reflex nervous influences and perhaps to alterations in the endocrine balance. Emotion may cause vomiting or diarrhea, and nervous exhaustion is a frequent cause of gastro-enteric disturbance. Organic disease of the heart or kidney may give rise to gastric symptoms. Nausea and vomiting often usher in acute infectious diseases, especially in children. Anaphylaxis may cause gastro-intestinal symptoms in persons who are hypersusceptible to certain protein foods. All these and many other conditions are frequently diagnosed incorrectly as "ptomain poisoning."

No reliance whatever can be placed on the taste, odor, or appearance of food. Many decomposed foods are considered savory and are known to be nutritious, but canned food that shows evidence of abnormal fermentation or putrefaction should not be eaten. It is not so much *decomposed* as *infected* food that may be harmful.

In order to prevent poisoning, food should be as fresh and clean as possible. When elaborately prepared, the methods must be satisfactory. If preserved by heat, the food must be made really sterile; if refrigerated, the temperature must be at or near the freezing-point; if pickled or preserved, the brine or sugar solution must be sufficiently concentrated to prevent bacterial growth. Furthermore, the health of food handlers, especially of those who handle milk and meat, is a significant factor.

The ultimate method of prevention is thorough cooking. The toxin of botulism is thermolabile, and the non-spore-bearing bacilli which cause food infection are also readily destroyed by heat. It takes a long time even for a high temperature to penetrate a joint of meat or a dish of spaghetti,

and as the responsible organisms grow well in cooked food, the cooking must be thorough and recent.

"PTOMAIN POISONING"

Ptomains are secondary cleavage products of protein putrefaction, and are ammonia substitution compounds. Most of them are inactive in the body or are no more poisonous than the corresponding ammonia salts. In composition they are chiefly amins, for the most part trimethylamins ($(CH_3)_3N$). The best known are sepsin, cadaverin, and putrescin. Those containing oxygen are the more poisonous. Vaughan defines a ptomain as a basic organic compound which is formed by the action of bacteria on nitrogenous material. On account of their basic properties ptomains react in some ways as do the vegetable alkaloids, and have consequently been called *putrefactive alkaloids*. The term "ptomain" includes substances which are very different chemically, and as the classification is not scientific it is gradually being abandoned. So-called "ptomain poisoning" is now recognized as infection with micro-organisms of the *Gaertner bacillus* group.

Leukomains are basic substances identical with or similar to the ptomains except that they are formed from the tissues of the living body by catabolism. The ptomains are derived from dead organic matter.

It is important to remember that ptomains, in sharp contradistinction to toxins, are non-specific. They are merely break-down products of the protein molecule and are elaborated by all bacteria or enzymes that are capable of producing a given degree of protein cleavage. Bacteria which are in no sense pathogenic may be capable of producing ptomains, while others which are highly pathogenic may produce few or none of these substances. Investigations which have been carried out to discover the nature of the toxic substance in ptomains have rendered the rôle of the ptomains themselves insignificant by demonstrating the bacterial origin of the poisoning.

The term "ptomain poisoning" is, therefore, a misnomer. Savage believes that it is quite incorrect, and Jordan states that it is used to decide an etiological uncertainty. All those who have recently studied the subject agree that the term should not be applied to food poisoning, since it is not so much *decomposed* as *infected* food that may be dangerous.

FOOD INFECTION

Definition.—Most so-called food poisoning with symptoms of gastro-intestinal irritation is an acute specific disease due to *Gaertner's bacillus* (*Bacillus enteritidis*) or to a closely allied species, such as *Bacillus paratyphosus B;* and is commonly miscalled "ptomain poisoning." Since the organisms are most often found in meat, the disturbance has often been called "meat poisoning"; but milk, cheese, and other milk products, as well as plant foods, may become infected.

Incidence.—The incidence of food poisoning rises markedly in summer, as does that of other intestinal infections. The bacilli responsible for the infection grow in food before it is eaten, and as their multiplication increases in hot weather the opportunity for transmission of infection by flies and in other ways also increases. Cases are not reported to have followed contact infection.

Most outbreaks are small, that is, only those individuals are attacked

who eat at a common board. The infection is especially associated with fraternity spreads, church picnics, and banquets, where the food is often prepared a long time in advance. The large outbreaks involving from one to two hundred persons can always be ascribed to milk.

Etiology.—The bacilli responsible for food infection belong to the *Gaertner group*. Since this occupies an intermediate position between the *colon bacillus* and the *typhoid bacillus*, it is called the "intermediate group." It is also known as the "hog cholera group," the "enteritidis group," the "paratyphoid group," and the "salmonella group." The classification of the various members is quite involved. They are all Gram-negative, aërobic, non-spore-forming, and do not ferment lactose. The more important are *Bacillus cholera suis*, *Bacillus suipestifer* (also called the hog-cholera bacillus), *Bacillus aertrycke* and *Bacillus paratyphosus B*. They apparently do not produce a toxin in food before it is eaten. The pathogenesis of the disease is similar to that of other acute, febrile, intestinal infections and is still not clearly understood.

Gaertner's bacillus and some of its congeners are pathogenic for some of our domestic animals as well as for man. The meat of cattle which suffer during life from this infection has frequently conveyed the infection to man. The flesh of healthy animals may become contaminated after slaughter by contact with unclean hands or with infected instruments. Human carriers of *Bacillus enteritidis* are unknown, but human carriers of *Bacillus paratyphosus* are occasionally found. In 4154 specimens of feces from healthy individuals examined in the author's laboratory in 1917–18 not a single carrier of any of these organisms which do not ferment lactose was found. Rats and mice harbor the *Bacillus suipestifer* and also the *Bacillus enteritidis* and become carriers. Hence, food may become infected by the feces and urine of rats and mice. There is abundant opportunity for such contact in slaughter-houses, butcher shops, refrigerator plants, or during transportation, and even in the home.

Although the food affected is not noticeably altered in appearance, taste, or smell, the idea that "poisonous" food must be tainted still persists. Contamination of food or water with bacilli of the Gaertner group cannot be recognized except by a skilled bacteriologist. It is, likewise, impossible to detect the typhoid bacillus, the dysentery bacillus, or the cholera vibrio except by laboratory methods. Meat, milk, or water may be teeming with these bacilli without being appreciably altered in taste, odor, or appearance.

Most outbreaks of food infection are due to meat, especially prepared meat foods, such as brawn, meat pies, sausage, chopped meat, salads, etc. The more food is handled and the longer it lies around, the greater the opportunity for it to become contaminated and for the bacteria to grow and multiply. The meat of the pig or ox caused 68 per cent. of the British and 61 per cent. of the Continental outbreaks. The almost complete absence of food poisoning as the result of eating the meat of sheep is striking. The number of cases ascribed to fish is small. Many outbreaks have been traced to infected milk or some milk product. A prodigious number of bacteria grow in meat and milk mixtures prepared some time before serving and allowed to stand at warm temperatures. Such mixtures may be responsible for trouble. Food infection caused by the bacilli of the Gaertner group is really an acute, self-limiting, specific disease with a definite symptomatology.

Symptoms.—Ordinarily, about six to twelve hours elapse between the ingestion of the infected food and the onset of symptoms. The *period of incubation* may, however, be as short as four hours or less, or as long as seventy-two hours or more. It varies in different outbreaks and also in the same outbreak. It is noteworthy that several meals may intervene between the ingestion of the infected food and the onset of symptoms. The food vomited at the onset is that to which symptoms are usually attributed, but is not necessarily the cause of the trouble.

The *symptoms* are essentially those of acute gastro-intestinal irritation, namely, nausea, vomiting, abdominal pain, and diarrhea. The onset is usually sudden. The attack may be ushered in with headache and a chill. Abdominal pain, which is frequently the first symptom, may be griping and severe. The diarrhea usually consists of the repeated passage of offensive stools. Later in the attack the feces become more watery and are frequently of a green color. The degree of faintness, muscular weakness, and prostration is about proportional to the severity of the gastro-intestinal disturbance. Thirst is noticeable. The temperature always rises, but seldom above 102° or 103° F. Various nervous manifestations, such as restlessness, muscular twitching, and drowsiness, may occur, but these are not constant or marked. Oliguria is often present. Herpes and other skin symptoms have been noted.

The severity of the attack varies greatly in different outbreaks and even in the same outbreak. The poisoning is sometimes fulminating and fatal within forty-eight hours, or merely causes slight diarrhea and malaise. The severe type may be choleraic in character and was formerly called *cholera morbus*. Usually the attack is mild, is over in a day or two, and recovery is prompt. The severity apparently depends upon the virulence of the infecting bacillus, the number of organisms ingested, the susceptibility of the individual, and other factors not understood. The death rate in 6190 cases studied by Savage was 1.5 per cent.

Diagnosis.—The diagnosis of food infection depends upon the history of exposure to the suspected food; symptoms suggestive of food poisoning; isolation of the infecting organisms from the suspected food and also from the blood, urine, feces, or viscera of the patient. Bacilli belonging to the Gaertner group disappear from the feces within seven to ten days after the appearance of symptoms. Agglutinins in the blood-serum can be detected six or eight days after the onset of symptoms. Agglutination in comparatively low dilutions is usually accepted as pathognomonic because it is unusual for the blood of a normal individual to react positively to *Bacillus enteritidis* or *Bacillus paratyphosus B*. Digestive upsets with acute gastro-intestinal disturbances are common and may be due to a great number of causes. As mistakes in diagnosis are frequently made, care should be exercised to exclude other factors.

Treatment.—There is no specific therapy; treatment is symptomatic. It varies with the age and strength of the patient; if the patient is an adult and of robust constitution, the treatment may be vigorous; in the case of a child, or any one much weakened by the attack, treatment should be conservative and even stimulating. It is first necessary to eliminate from the system all the supposed injurious material by emesis or lavage, purgation, or diuresis. Vomiting should be favored. An emetic, as mustard (1 tablespoonful in $\frac{1}{2}$ tumblerful of warm water), may be administered early in

the disease if there is nausea and no vomiting. It is advisable to wash the stomach with warm, normal saline solution until the washings are clear. For the abdominal pains, local applications should be made, such as hot fomentations, turpentine stupes, or flax-seed poultices. These are soothing and may give relief if the pain is not too severe. If, however, the pain is very acute, hypodermic injection of a small dose of morphin ($\frac{1}{6}$ to $\frac{1}{4}$ grain) may be necessary. As this may mask the symptoms of some serious abdominal condition, it should be administered only with care.

Practically nothing should be given by mouth during the acute attack except cracked ice, sips of whey, barley or oatmeal water, or albumin water. If there is collapse, stimulants may be used. No solid food should be taken until all symptoms of gastric irritability have subsided. When considerable diarrhea persists, bismuth subcarbonate (15 grains) in mucilage of acacia, may be given every two or three hours. If this condition continues, a mild astringent with or without small doses of codein is advisable.

It is important to keep in mind the medicolegal aspects of food infection and to save samples of the suspected food, as well as of the stools, blood, urine, and for examination by a competent analyst.

BOTULISM

(*Allantiasis, Food Intoxication*)

Botulism is an acute poisoning caused by the toxin of the *Bacillus botulinus*.[1] It occurs both in man and animals. The bacillus grows and produces its toxin in food before it is eaten. The name botulism (from *botulus*, sausage) has lost its original significance because the intoxication is produced not by a single type of food, but by the bacillus which grows in a great variety of food-stuffs of both animal and plant origin.

Incidence.—A total of 91 outbreaks of botulism has been reported in the United States and Canada since 1899, involving 345 persons, and causing 213 deaths, a death rate of 61.7 per cent. Only 30 of these 91 outbreaks were proved bacteriologically to be true botulism. Of 82 of these outbreaks, 63 were due to plant foods and 19 to animal products.

The distribution of the disease is focal. Since 1889 a total of 45 instances of human botulism have been reported from California, involving 132 persons, with 81 deaths. The frequent occurrence of botulism in southern California seems closely connected with the distribution of *Bacillus botulinus* spores in the soil.

Botulism in Animals.—*Limberneck* in chickens, turkeys, and ducks is caused by the accidental or experimental ingestion of spoiled food containing the toxin of *Bacillus botulinus*. Limberneck is a symptom due to weakness or paralysis of the muscles of the neck. Fowl get the disease from the larvæ of the green fly, *Lucilia cæsar*, after it is contaminated with carrion flesh. One of the methods used to determine the presence of toxin in spoiled food is to feed it to chickens. Forage poisoning in horses is sometimes true botulism, and may be due to eating moldy silage. Many animals are susceptible—guinea-pigs, rabbits, mice, cattle, monkeys, goats, etc.

Etiology.—The disease has been known clinically by German physicians since 1735. The *Bacillus botulinus* was discovered by van Ermengem, who in 1895 described a series of cases which occurred in Ellezelles, Belgium.

[1] *Clostridium botulinum* according to the new nomenclature.

A complete history of the condition and a review of the literature up to 1918 will be found in Dickson's monograph.

Bacteriology.—*Bacillus botulinus* is a spore-bearing anaërobe which grows well both in the incubator and at room temperature. The name is applied not to a single organism, but to a group. There are at least three and probably more types. Type *A* produces a strong toxin and is especially associated with the disease in America. Type *B* seems to be more widely scattered, and while sometimes responsible for the disease in the United States, is found more often in Europe. Of a series of outbreaks studied bacteriologically in the United States, 23 were found to be due to Type *A* and only 3 to Type *B*. Both strains of organisms may cause botulism in animals as well as in man. Type *C*, recently isolated by Bengston, is not known to be toxic to man. Some forms of "fish poisoning," especially those reported in Japan, as well as the parabotulism of cattle in South Africa, are probably types of botulism.

The symptoms produced by the various types of *Bacillus botulinus* are similar; the pathology, treatment, and prevention, alike. Because the toxin and antitoxin for each type are specific, it is necessary to vary the antitoxin with the infection or to use a polyvalent serum for the prevention or treatment of the disease.

Habitat and Distribution.—*Bacillus botulinus* is essentially a soil organism, and is found in many parts of the world, even in the virgin soil of mountains. The spores are widely distributed in nature. They are found in soil, on fruit and vegetables, in the larvæ of worms, in dust, and in the intestinal tract of herbivoræ. Consequently, they are present almost everywhere in dust, dirt, and carrion. The habitat resembles in all respects that of other intestinal, spore-bearing anaërobes, such as the tetanus and the gas bacilli.

Thermal Death Curve of the Spore.—The spores of *Bacillus botulinus* are very resistant to heat and to germicides. They may live five hours in boiling water, but are killed in fifteen minutes at 110° C. and in six minutes at 120° C. These are important facts in connection with the preservation of food. To be entirely safe, canned food should be heated sufficiently high and sufficiently long to kill botulinus spores. The bacillus itself is readily destroyed by heat; the toxin is also thermolabile.

Botulinus Toxin.—The toxin of *Bacillus botulinus* is an exotoxin, differing from the poisons of diphtheria and tetanus in that it is poisonous when ingested. It is a true toxin because: (1) it produces the symptoms and essential lesions of the disease; (2) it is readily soluble; (3) it is very specific; (4) it acts only after a period of incubation; (5) it is thermolabile (destroyed at 75° C. in ten minutes); (6) it produces an antitoxin. As it acts especially upon the central nervous system, it is a *neurotoxin*. Every strain of *Bacillus botulinus* does not produce a potent toxin; each type produces a poison that is neutralized only by a specific antitoxin.

Botulinus toxin is exceedingly poisonous. As small an amount as 0.000,001 c.c. kills a 250-gram guinea-pig in three to four days. The poisonous food need not necessarily be swallowed; fatal poisoning in man has been reported to follow simply tasting or nibbling.

Foods Involved.—Almost any protein-containing food in which the organism grows may be responsible for botulism, and the disease is, therefore, caused by a great variety of plant and animal food products. In the

United States it has usually been associated with plant foods, whereas in Europe it is caused especially by meat products, particularly sausage and pork, and by fish. The foods that have been incriminated are olives, spinach, beans, beets, corn, ham, sausage, and cottage cheese. A large percentage of the outbreaks is due to foods preserved at home, although sometimes commercially canned products are infected. As the bacillus does not grow and multiply in acid media, foods having a *p*H below 5.4 are immune. This doubtless explains why botulism is practically never associated with fruit. Strong brine (8 per cent. or more) and also sugar in sufficient concentration (at least 50 per cent.) inhibit the growth of the bacillus and prevent the formation of the toxin.

Morbid Anatomy.—There are no characteristic gross lesions in botulism. The only constant findings are marked congestion of the central nervous system and of the abdominal and thoracic viscera. There may be multiple hemorrhages about the base of the brain and upper part of the cord, and the brain tissues may be edematous and show scattered hemorrhages. The lungs are congested and often show areas of bronchopneumonia. The heart muscle is soft and flabby; the liver, kidney, and spleen are hyperemic and all the parenchymatous organs are opaque and cloudy on section. There may be ecchymoses and hemorrhages on the serous surfaces and in the lungs. Ophüls described cellular thrombi, but these may not occur when the illness is of short duration. Dickson states that, while suggestive, they cannot be considered as pathognomonic of botulism. In a series of necropsies on 12 human subjects the tissues of 9 were found to contain typical thrombi. There is no destruction of the ganglion-cells such as was described by Marinesco. Geiger points out that in microscopic diagnosis there should be no confusion between botulism and epidemic encephalitis, since perivascular lymphocytic infiltration is not a characteristic lesion of the former.

Symptoms.—Botulism is a true bacterial intoxication and stands alone as a type of food poisoning. The disease is characterized by weakness or paralysis of the muscles, absence of fever, and high death rate. Gastro-intestinal symptoms, which are prominent in food infection, are usually absent in botulism, in which constipation is the rule.

The symptoms usually appear from eighteen to thirty-six hours after the ingestion of the poisonous food. In one case symptoms were reported in two hours and in another in four hours. When the symptoms occur very early, they are of the acute gastro-intestinal type and probably are due to some other irritating factor in the food. Occasionally the period of incubation is prolonged up to the eighth day.

When gastro-intestinal symptoms develop they appear early, are transient, and not pronounced. The patient may complain of burning and distress in the region of the stomach, and there may be nausea and vomiting with or without diarrhea. As a rule these symptoms, which usually persist for a few hours or at most a day or two, are followed by constipation. Frequently there is distention of the intestines.

The earliest symptom in most cases is a peculiar indefinite lassitude and fatigue, and sometimes dizziness or headache which the patient often attributes to constipation. Disturbances of vision occur very early and are often the first indication of trouble. There may be scintillation and dimness of vision because of loss of accommodation. Early involvement

of the third cranial nerve is indicated by blepharoptosis, mydriasis, loss of the reflex response to light, and diplopia. Strabismus, nystagmus, and vertigo are not uncommon, and photophobia has been recorded in a few cases. Difficulty in swallowing and talking soon appears and the patients often complain of a sensation of constriction of the throat. The tongue is heavily coated and the breath foul. The mucous membrane of the mouth and throat is dry. Attempts to swallow frequently induce spells of strangling which may be very severe and persist until the patient is exhausted. Regurgitation of fluid through the nose and insufflation into the trachea frequently occur during this strangling.

General muscular weakness soon comes on. In severe cases the muscles are completely relaxed and the patient is unable to raise arms or legs from the bed. Complete paralysis rarely occurs. Inco-ordination is common. There is *complete absence of sensory disturbances* and practically *no pain*. The mind remains clear until a short time before death. There is no special change in the urine except that the amount depends upon the fluid intake. Usually there is anuria on account of the difficulty of swallowing liquids.

The temperature is usually subnormal, 96° to 98.6° F., and, in uncomplicated cases, remains low during the whole illness.

The pulse is at first slow, then rapid. The blood-pressure is 80 to 90 mm. of Hg diastolic and 120 to 140 systolic. Late in the course of the disease breathing becomes difficult and labored and there may be extreme dyspnea and cyanosis. The most frequent cause of death is respiratory failure. There is no particular change in the blood-picture or the cerebrospinal fluid.

Diagnosis.—The mere presence of *Bacillus botulinus* is not satisfactory proof of the disease, for the spores are ubiquitous in soil and on vegetables. The toxin may be readily demonstrated by injecting the suspected material into susceptible animals. The spores can be isolated by appropriate bacteriological methods. The symptoms of the disease are usually sufficiently characteristic.

There is a sharp contrast between food infection and food intoxication, as is shown in the following table:

Food Infection.	*Food Intoxication*
Often miscalled *"ptomain poisoning."*	*Botulism*—sausage poisoning.
Cause: An infection with *B. enteritidis* or closely allied bacilli.	A poisoning caused by the toxin of *B. botulinus*.
The bacteria grow in the food, but do not form a toxin in the food.	A true toxin is preformed in the food.
Resembles an acute self-limiting infectious disease.	An acute poisoning with a neurotoxin.
Gastro-intestinal symptoms the chief manifestation.	Gastro-intestinal symptoms usually absent.
Diarrhea.	Constipation.
Cramps.	No pain.
Fever.	No fever.
No paralysis.	Muscular weakness and paralysis a constant feature.
No disturbances of vision.	Ophthalmoplegia.
Summer prevalence like other intestinal infections.	No particular season.
Low death rate—at most 1.5 per cent.	High death rate—60 to 100 per cent.
Convalescence rapid.	Convalescence slow.
Chiefly conveyed in meat or milk.	Conveyed in almost any food of plant or animal origin.
No specific therapy.	Antitoxin.

Prognosis.—The death rate in botulism is high (in the United States 61.7 per cent.) and surprisingly uniform. There is a direct correlation between the severity of the poisoning and the period of incubation. A short incubation period indicates that the intoxication is severe and often that it will be fatal. In a series of 246 cases collected by Geiger, of which 173 resulted fatally, 147, or 85 per cent., of the deaths followed a period of incubation of less than forty-eight hours.

The disease is usually of brief duration. The majority of victims die within from three to six days after ingestion of the poisonous food. If the patient lives ten days, he is apt to recover. Convalescence is extremely slow and tedious. Disturbances of vision may persist for months, but there are no permanent sequelæ.

Treatment.—*Botulinus antitoxin* is a specific preventive, but has limited curative value. Like other antitoxins, such as those of diphtheria and tetanus, it must be administered early to be effective. It is possible to save susceptible animals by the injection of botulinus antitoxin even though definite symptoms of intoxication are manifest, but not after respiratory symptoms have developed. The antitoxin should, therefore, be administered as soon as the diagnosis is made, even though it does no more than prevent further harm. If the type of botulism has been determined, the homologous antitoxin should be used; otherwise, a polyvalent serum or both Types *A* and *B* should be injected without delay. If it is necessary to wait for the antitoxin, the patient should be kept under full influence of morphin, for in the experimental disease it has been found that this delays the toxic action. Alcohol is not effective for this purpose, although it detoxicates the poison when brought in direct contact with it. Thus it has been noted that persons who took alcohol with the food containing the poisonous material escaped botulism. The remaining treatment of the disease is supportive and symptomatic.

Edmunds and Long find that botulism is a curare-like paralysis of the endings of the motor nerves going to the voluntary muscles. On the basis of this experimental work it is recommended that artificial respiration be instituted when respiration shows signs of failure, if necessary by means of bellows and a tracheal cannula. The careful administration of physostigmin may be tried, although it is not a physiological antidote.

OTHER CAUSES OF INJURY DUE TO FOOD

Food may be injurious for reasons other than infection or intoxication.

Food allergy is rather common. Many persons are hypersusceptible to some particular article of diet, such as shell-fish, fish, strawberries, tomatoes, pork, cereals, eggs, and milk. The list of disturbing foods is very long, and includes many protein substances. When there is difficulty in determining which food is responsible, the skin test may be employed. Fish, tomatoes, and cheese are apt to produce urticaria; cereals, pork, and milk, erythema and eczema; and eggs, asthmatic symptoms. There is, however, no constancy in this respect. The symptoms produced are mainly vasomotor disturbances, skin eruptions, gastro-intestinal disorders, and respiratory difficulties. Collapse may result within a few minutes from the ingestion of a very small amount of the substance to which a person is hypersusceptible. In most cases the susceptibility is clearly inherited, but in some it may be acquired.

The attacks are often mistakenly diagnosed "ptomain poisoning," for they are sometimes accompanied with vomiting, diarrhea, and collapse. *The fault is clearly not in the food but in the person.* The food itself may be good, nutritious, clean, and satisfactory, but the person lacks the mechanism to digest and assimilate certain substances normally. This is a good example of the saying that "one man's meat is another man's poison." Anti-anaphylaxis to this condition may be brought about by administering increasing doses of the responsible antigen by mouth. The amount given at first must be minute, for it should not produce symptoms; it may then be increased cautiously and very gradually. This treatment should be continued a long time. The course must sometimes be repeated.

Natural Poisons.—The tissues of many plants and a few animals are naturally poisonous. Certain mushrooms and a few higher plants are sometimes mistaken for food, especially by children and the ignorant. Three beans of the castor plant, containing ricin, may prove fatal to a child. Of the mushrooms, Amanita and Volvaria are those usually involved in fatal accidents. A historic incident of mushroom poisoning occurred in the family of the Greek poet Euripides, who lost in one day wife, daughter, and two sons.

Few fish containing physiological or natural poisons are found outside of the tropics. At the spawning season, however, the roe of different members of the sturgeon family, of the pike, and of the barbel have been said to cause serious and even fatal intoxication. Mussels may perhaps contain a poison known as mytelotoxin. Some fish, such as the fugu, puffers, balloon fish, and globe fish, are always poisonous. The fugu is so toxic that it is sometimes eaten for suicidal purposes in Japan.

Accidental Poisons.—Poisons sometimes get into food and produce gastro-intestinal disturbances. Irritating substances, such as arsenic, caustic alkalies, roach powders, and rat poisons, occasionally cause trouble by design or accident. Insect powders have been mistaken for baking powders. The writer investigated one case in which a caustic lye compound used for washing was left in a coffee urn by the scullery maid. Persons who drank the beverage vomited, suffered from cramps, and were reported to have "ptomain poisoning."

Special Poisons.—*Ergotism* is a form of food poisoning brought on by prolonged use of meal made from grain contaminated with the *Claviceps purpurea.* The fungus develops in the flowers of rye and other grains. The disease may have an acute or chronic course and be characterized by symptoms which are nervous or convulsive, or trophic or gangrenous in character. Ergotism is practically unknown in this country, but in Europe is still seen, although not as frequently as in former times.

Lathyrism, or vetch poisoning, occurs in some parts of Europe—notably Austria and Italy—in northern Africa, and in India. The vetch seed is ground in the form of meal and used as a partial substitute for wheat. The seed is popularly known as chick-pea. The symptoms are sudden and severe pain in the lumbar region, girdle sensation, motor paralysis of the lower extremities, tremor, and fever. The nature of the poisoning is not known.

Solanin poisoning, attributed to potatoes, has occurred especially among troops. Old sprouting potatoes and sometimes potato salad have been thought to be the cause. The symptoms reported are headache, abdominal

pain, nausea, vomiting, diarrhea, prostration, dizziness, and slight delirium. Fever has usually been absent. The symptoms only rarely become threatening, and recovery is rapid in practically all instances. It is now recognized that some outbreaks, at least, are caused by bacterial infection and not by the potato itself.

Faulty Diet.—There are many other ways in which food may injure health. The amount or kind may not be suitable and the food intake may be unbalanced. *Deficiency diseases*, such as scurvy, beriberi, pellagra, and possibly others, are of dietetic origin. Good wholesome food is one of the prime factors in hygienic living. A generous diet of good food is useful in the prevention and cure of disease. Food is nature's most substantial tonic and is the chief factor in stimulating growth.

Deranged Function.—Gastro-intestinal disturbances with symptoms resembling food poisoning may simply be the result of deranged function. The chief causes are eating too fast, eating too much, eating injudicious mixtures, and eating when fatigued. Unripe fruit and undercooked vegetables frequently cause gastro-intestinal upsets. Many other factors are responsible for acute gastro-intestinal symptoms, chief among which are emotion and exposure to cold and wet.

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REFERENCE

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DEFICIENCY DISEASES

PELLAGRA

Definition.—Pellagra is a disease generally attributed to a food deficiency, and is characterized clinically by skin lesions, gastro-intestinal disturbances, nervous and mental changes, and periodic seasonal variations.

Historical.—This disease was first accurately described by the Spanish physician, Gaspar Casal, in 1735 as *mal de la rosa*. It was subsequently described in Italy, in 1771, by Francisco Frapolli, who first applied the name *pellagra* (rough skin). Its wide-spread occurrence in northern Italy about this time is evidenced by the establishment in Milan of a hospital for the treatment of pellagra, under the direction of Gaetano Strombio, whose authoritative work, *De Pellagra*, appeared in three volumes during the years 1786-1789.

Incidence.—Pellagra is a common disease in southern Europe, Egypt, India, Central America, and the West Indies. While an occasional sporadic case had been reported in the United States during the nineteenth century, its surprising appearance in endemic form in this country in recent years has brought about an extraordinary interest in the study of the disease. The first definite outbreak in the United States was reported in 1907 by George H. Searcy, of Alabama. For the next eight years the incidence of the disease increased at an alarming rate. Since 1915, however, there has been a very striking disappearance of pellagra, although isolated cases are not infrequent. The outbreak in the United States was further characterized by the acute nature of the disease, which ran a rapidly fatal course, and by its wide-spread distribution among various classes. In other countries pellagra had been regarded as an essentially chronic malady confined almost entirely to the poorer classes in rural communities. The incidence of pellagra among the inmates of orphanages, almshouses, and asylums was also rather striking in the American epidemic.

Pellagra may occur at all *ages*, but the majority of cases appear in the third and fourth decades of life. *Women* appear to be slightly more susceptible than men. The disease affects the *white* and *negro races* in about equal proportion, but the mortality is higher among negroes.

Occupation.—Pellagra has been regarded as a disease essentially of the poorer classes, but this is not wholly true in the United States.

Season.—The onset of the disease as well as the recurrences are apt to be somewhat more frequent in the spring than in the fall.

Etiology.—The cause of pellagra is unknown. There are three general etiological theories: (1) that the disease is due to a preponderance of maize (cornmeal), or to the use of spoiled maize, in the diet; (2) that pellagra is an infectious disease due to a specific organism which has not yet been isolated, but which may be transmitted directly or through the agency of some fly or insect; and (3) that pellagra, as well as scurvy and beriberi, is one of the food deficiency diseases, caused either by a specific lack of an essential substance (vitamin) or by a poorly balanced diet of low protein content. The view more generally accepted today is that pellagra is a nutritional disease resulting from a lack of proper food balance. The experimental work of Joseph Goldberger and his co-workers, of the

United States Public Health Service, leads to the conclusion that: (1) pellagra is essentially of dietary origin; (2) it depends on some undetermined lack in a diet consisting of disproportionately small quantities of animal or leguminous protein and disproportionately large quantities of vegetables; and (3) pellagra does not develop in individuals who consume a mixed, well-balanced, and varied diet. The practising physician encounters pellagra among well-to-do patients chiefly when the diet has been restricted because of some real or fancied digestive disorder, but occasionally when such inordinate amounts of whisky (not necessarily corn liquor) have been taken that relatively little food has been eaten for long periods. Finally, clinical observation in many cases seems to indicate that pellagra is not apt to be a primary disease, but occurs secondarily in persons who already suffer from some chronic disease, such as syphilis, tuberculosis, or other infections.

Morbid Anatomy.—There are no pathological findings that are distinctive of this disease. The tongue may exhibit exfoliation or ulceration, or an atrophic glossitis with a red, smooth surface. The salivary glands are often enlarged. Acute esophagitis may occur. Atrophy of the muscular coats of the stomach and intestines is seen in a large proportion of the cases and the mucosa may be hyperemic and show petechial hemorrhages. Occasionally ulceration is noted in the jejunum and ileum. The liver is large and pale. The ganglion-cells of the brain and spinal cord may undergo varying degrees of degeneration. The posterior and lateral columns of the cord are especially liable to degenerative changes. The skin changes are characterized by an erythema or a dermatitis which may lead to definite atrophic changes.

Symptoms.—The disease usually begins in the spring, but occasionally in the autumn. Certain *prodromal symptoms* are very characteristic, but, as they occur two or three months before the appearance of the eruption, they are likely to be misinterpreted. They consist of vague digestive disturbances with loss of appetite and possibly slight diarrhea, mental depression, headache, vertigo, and insomnia.

Skin.—The eruption generally begins on the back of the hands as an erythema resembling ordinary sunburn. The forehead, neck, and feet may also be involved. The skin over the affected areas may gradually become darker and then desquamate, or the appearance of vesicles and bullæ may be followed by cracking of the skin and secondary pyogenic infection. The skin lesions persist for a few days or several weeks and tend, in chronic cases, to recur each spring or fall. The end-result is usually an atrophic scarring, so that the skin, especially over the back of the hands, may have a parchment-like texture and a dull red color. Certain features of the skin lesions in pellagra are distinctive. They are symmetrical in location on the body surface and apt to be sharply defined. A certain amount of pigmentation occurs and even after the dermatitis subsides a pigmented hyperkeratotic border may remain. The erythema usually appears only on parts of the body which are exposed to the light, but occasionally symmetrically placed lesions are found on protected parts.

Digestive Tract.—The two chief symptoms referable to the digestive tract are stomatitis and diarrhea. Occasionally sore mouth is the first symptom to suggest pellagra. The mucous membrane of the tongue and buccal cavity becomes very red, at times raw, and may be ulcerated. Especially with *achylia gastrica* the tongue is very apt to be clean with red edges, or

beet red, very clean, and bald (atrophic glossitis). A distressing salivation may accompany the stomatitis, particularly when there is no free hydrochloric acid in the stomach.

Persistent or recurring diarrhea develops in about 75 per cent. of the cases of pellagra. The bowels may, however, be regular or constipated. There is nothing characteristic in the diarrheal stools. They are generally frequent and watery, may contain undigested food, and occasionally blood. As a rule, there is no marked pain, but in certain cases tenesmus may be distressing. Analysis of the gastric contents during pellagra shows an achlorhydria in about 40 per cent. of the patients, and it is in these cases, particularly, that the stomatitis and diarrhea may be most marked. Loss of appetite, nausea, and vomiting are often prominent symptoms.

Nervous System.—Subjective complaints are very common, especially headache, dizziness, depression, and sleeplessness. Mental changes ensue in probably one-third of the cases and may consist of apprehension, irritability, confusion, hallucinations, and delusions, or actual dementia. Paresthesias, tremors, and muscular cramps are common. The symptoms produced by the changes in the spinal cord vary with the relative degree of involvement of the lateral and posterior columns. The deep reflexes may be unaffected, or there may be a spastic paraplegia with exaggeration of the deep reflexes; in other cases a flaccid paralysis ensues and the deep reflexes are absent. These signs of changes in the pyramidal tract are characteristic of combined sclerosis of the spinal cord, and recent reports indicate that they occur only in patients with persistent achylia gastrica.

The blood shows no characteristic changes except a moderate secondary anemia. The spinal fluid is unaltered. The temperature is normal, as a rule, but fever may occur in the acute cases.

Diagnosis.—There is no difficulty in recognizing typical pellagra with stomatitis, diarrhea, and symmetrical dermatitis on the exposed portions of the body. Nervous and mental changes may be lacking, but the diagnosis of pellagra should rarely, if ever, be made in the absence of skin lesions or a definite history of the characteristic erythema. Cases of so-called "*pellagra sine pellagra*" have been described, but it should be understood that certain individuals with persistent achylia gastrica may develop atrophic glossitis and chronic or recurring diarrhea with subsequent combined spinal sclerosis. *Endemic sprue* may be confused with pellagra, but lacks the skin lesions, and may be expected to show the characteristic fatty stools. Acute pellagra may persist only for weeks, whereas the chronic form may continue for years, with recurrent manifestations in the spring or the fall. Each succeeding attack tends to be more severe than the former one.

Prognosis.—The outcome often depends on the primary condition or disease to which pellagra is secondary. In the acute pellagra, which has been so relatively frequent in the United States, the prognosis is very unfavorable. Erythema of the moist type, toxic manifestations, marked mental changes, and inability to retain adequate nourishment are generally regarded as ominous signs. The outlook is best in the chronic cases without mental changes.

Treatment.—The prophylaxis as well as the treatment of the disease appear to be largely a problem of nutrition and of eradication of any underlying disease. It is impossible to conceive that a healthy subject on a

well-balanced diet would develop pellagra. Pellagra is particularly apt to thrive after amebiasis, uncinariasis, malaria, tuberculosis, tertiary syphilis, and chronic alcoholism, and after chronic or recurring "indigestion" secondary to chronic appendicitis, chronic cholecystitis, and especially achylia gastrica.

The diet in pellagra should be general, varied, and well balanced as regards the proportion of protein, carbohydrate, and fat. Meat, eggs, and milk are essential, but should be supplemented by vegetables and fruits. Past experiences in asylums and institutions have emphasized the real danger of a monotonous diet containing an excess of carbohydrate.

Rest in bed is essential during the acute stages and intelligent *nursing* is most important to prevent bed-sores and secondary pyogenic infection, to institute proper hygiene of the mouth, and to see that the patient takes adequate nourishment. Of the many *drugs* which have been tried out thoroughly, only two appear to be of real value—arsenic and hydrochloric acid. Arsenic is probably best administered in the form of Fowler's solution by mouth, but it may also be injected hypodermically in the form of cacodylate of soda, or intravenously as arsphenamin. Overdosage should be carefully avoided in order to prevent an arsenical neuritis that may confuse the clinical picture. The administration of hydrochloric acid is frequently followed by brilliant results in the relatively large number of pellagra patients with achlorhydria, and in such cases the stomatitis and diarrhea may quickly subside. Adequate doses are essential; the official dilute hydrochloric acid should be given with meals in doses of 1 teaspoonful mixed with 6 or 8 ounces of buttermilk or orangeade. Change of scene and climate is to be recommended when possible, but institutional care may be necessary if patients have mental symptoms.

DOUGLAS VANDERHOOF.

BERIBERI

Definition.—Beriberi is a deficiency disease due to the lack of certain accessory food substances (vitamin *B*) in the diet. It is characterized clinically by multiple neuritis, edema, and cardiac weakness.

History.—It is a disease of great antiquity and has been endemic for centuries in the Orient and certain tropical countries. Like scurvy, beriberi breaks out especially on ships and in jails, barracks, and asylums. During the Russian-Japanese War over 80,000 cases of beriberi developed in the Japanese Army in a period of two years. It is recognized that beriberi is constantly present in all countries where rice is the staple article of diet.

Etiology.—From a maze of conflicting theories it has finally become recognized that beriberi, like other deficiency diseases, is associated with an ill-balanced and monotonous diet. The term "vitamin," introduced by Funk, is now applied to certain accessory food substances that are of vital importance in nutrition. Fat-soluble vitamin *A* is antirachitic and is found in cod-liver oil and other animal fats and in various meats and certain vegetables. Water-soluble vitamin *B* is antineuritic and is present in the

bran layers of cereals, in peas and beans and yeast, and in milk, eggs, and various meats. Water-soluble vitamin *C* is antiscorbutic and is found in fresh vegetables and fruits, and to some extent in fresh meats. A temperature of 212° F. (100° C.) does not seriously impair vitamins, but higher temperatures such as are used in sterilizing and canning foods destroy them. The essential etiological factor in most cases of beriberi is too exclusive restriction of the diet to polished rice, *i. e.*, rice from which the external layers have been completely removed by a process of overmilling. The disease may develop also when a monotonous diet is limited to other grains that have been decorticated, such as wheat and corn, as well as when it consists chiefly of bread made from fine flour, and sugars, molasses, honey, and fats, all of which are deficient in the antineuritic vitamin. The extensive use of canned foods, as on shipboard, also favors the occurrence of the disease. Beriberi has been especially prevalent in the past among the soldiers and sailors of oriental countries. It continues to take very heavy toll among the poorer and more ignorant natives. The majority of cases occur in young adults, but the disease may affect the babies of beriberi mothers. The incidence is greater in males than in females.

Morbid Anatomy.—The characteristic findings at necropsy consist of a combination of degenerative nerve lesions, enlargement of the right heart, anasarca without nephritis, and chronic passive congestion of the abdominal viscera. All of the peripheral nerves show changes which may vary from a slight medullary degeneration of a few fibers to an almost complete destruction of the nerve trunk. Similar degenerative lesions are also found in the cells of the anterior horn and the posterior ganglia of the spinal cord. Disintegration of certain brain cells with proliferation of neuroglia has been reported, although there are no mental symptoms to correspond with such changes. The skeletal muscles are wasted and show diffuse parenchymatous degeneration. The heart is enlarged, the hypertrophy and dilatation being especially evident on the right side. Histologically the myocardium shows evidences of fragmentation with hyaline and fatty degeneration. Anasarca and effusion in the serous cavities, most frequently hydropericardium, are relatively common findings, although in all cases the lesions are not of this wet type. Chronic passive congestion of the abdominal viscera is very common, and the mucosa of the stomach and duodenum is generally congested and ecchymotic.

Symptoms.—Experiments on fowls placed on a diet lacking the antineuritic vitamin have shown that degenerative lesions in the peripheral nerves can be demonstrated after seven days. Strict feeding experiments on human beings, however, indicate that a depletion period of three months must elapse before clinical symptoms arise. On a diet in which the antineuritic vitamin is insufficient, but not entirely lacking, the disease ensues in just as severe a form, but the depletion period is considerably lengthened.

Three types of beriberi are recognized: (1) Dry beriberi, in which the symptoms are referable principally to the nervous system; (2) wet beriberi, in which the symptoms consist chiefly of generalized edema and serous effusions; and (3) acute (or pernicious) beriberi, in which serious heart symptoms develop early and in which sudden death may ensue.

The *onset* of the disease is insidious with malaise, heaviness in the legs, mild gastro-intestinal disturbances, palpitation of the heart, and possibly shortness of breath on exertion. Definite neuritis soon develops with

paresthesias, soreness of the muscles, and sensitiveness of the nerve trunks, with some loss of cutaneous sensation and diminution of the deep reflexes. About the same time the legs become edematous. The patient may remain in just this condition for months or years (so-called *rudimentary beriberi*) or sudden heart failure may occur. As a rule, however, the disease *progresses* with a flaccid paresis and muscular wasting. The edema, which is almost always present, may vary from a slight pretibial swelling to a general anasarca. Serous effusions take place in the pericardium and the pleural cavities, while ascites is much less frequent. There may be a foot-drop with steppage gait, or marked ataxia. The deep reflexes are greatly diminished or absent and the electrical reaction of degeneration follows. The heart is almost always enlarged and the patient suffers from precordial pain, palpitation, dyspnea, and epigastric distress. Aphonia may result from paralysis of the vocal cords. Mental symptoms are generally lacking except for occasional states of confusion similar to Korsakow's syndrome which occurs in alcoholic neuritis. The vasomotor apparatus gives indication of lowered tone with relatively low blood-pressure. Fever does not occur in uncomplicated cases. The blood may show a slight secondary anemia. The urine is generally normal.

Diagnosis.—The combination of peripheral neuritis, edema, and myocardial weakness with enlargement of the heart is characteristic of no disease other than beriberi. Multiple neuritis from alcohol, lead, or arsenic is not accompanied by edema, whereas heart disease and nephritis are rarely complicated by neuritis. In so-called nutritional edema, or "war dropsy," which apparently results from living on a diet containing insufficient protein and excess of fluid and salt, polyneuritis is not common. A study of the dietary factor in beriberi with a knowledge of foods that lack the essential antineuritic vitamin is, of course, most important in the recognition of the disease. In order to detect the milder, ambulatory forms of the disease among groups of men in barracks, prisons, or on shipboard, in whom the possibility of a sudden cardiac death is always possible, Vedder recommends the following tests: (1) Squeeze the muscles of the calf to detect tenderness; (2) test the anterior surface of the leg for areas of anesthesia with a pin; (3) test the patellar reflex which is apt to be diminished or absent on one or both sides; and (4) make the patient squat on his heels after the oriental manner of sitting; if he is suffering from beriberi this may cause pain and there may be inability to rise without using the hands.

Prognosis.—The mortality rate varies greatly in different outbreaks and in different localities, and depends largely on the character of the diet and the efficacy of measures to control the disease. The average death rate is from 3 to 5 per cent. The possibility of sudden death should be considered even in mild cases of the disease. In patients with extensive neuritis recovery is slow and tedious even when the diet is ideal, and full recovery may require some months.

Treatment.—The *prophylactic treatment* is most important, as beriberi is a preventable disease. Among bodies of troops and in institutions, where the rations can be prescribed and controlled, beriberi can be entirely eradicated. Among the great mass of the ignorant populace in the endemic foci the problem of prevention is very serious and can only be solved by a slow process of education. This is rendered the more difficult by racial food habits and extreme poverty. In the occasional outbreaks of beriberi in

certain institutions in the United States and Europe the disease has resulted from a too exclusive restriction of the diet to white bread and molasses. The prevention of beriberi is summed up by Vedder as follows: (1) If rice forms the main staple of diet, it should be undermilled. Similarly, when bread is the staple, it should be made of whole wheat flour. (2) Beans, peas, or some similar legume should be served at least once a week. (3) Whole barley should be used in all soups. (4) Fresh meat should be served once daily if possible; eggs and fresh milk as freely as possible, and whenever meat is not provided. (5) The excessive use of canned foods is to be avoided.

The *treatment of the disease* itself is almost entirely dietetic. A full and varied diet is essential with special inclusion of foods known to be rich in the antineuritic vitamin. In the Orient, where the populace is as dependent on rice as are other races on bread and potatoes, only undermilled or whole rice should be permitted. Rice polish, wheat bran, and yeast are rich in antineuritic vitamin and should supplement a full general diet. Meat, eggs, fresh milk, and vegetables should be used freely.

The use of *drugs* is purely symptomatic. The saline cathartics are indicated in the cases with marked edema. Absolute rest in bed is essential for all patients showing any evidence of heart weakness and digitalis should be used freely and in adequate doses. Strychnin has been used extensively, as in other forms of neuritis, and in experiments on fowls has seemed to prolong life. Serous effusions should be relieved by aspiration. Prompt venesection in sudden cardiac failure has proved to be of real value by relieving venous congestion and acute cardiac dilatation. At the same time full doses of morphin and caffein should be administered hypodermically. During convalescence, massage, electricity, and graduated exercises should be employed to restore the wasted muscles.

Douglas Vanderhoof.

SCURVY

Definition.—Scurvy is a disorder of nutrition due primarily to the lack of a specific vitamin. When it occurs in infants it is termed "Barlow's disease." It is characterized by distinctive changes in the bones and by lesions of the blood-vessels; these give rise respectively to bone tenderness and to hemorrhages in various parts of the body.

History.—It is difficult to define with precision the earliest description of scurvy. Hippocrates refers to it as attacking the soldiers and de Joinville gives a vivid description of its inroads among the Crusaders about the middle of the thirteenth century. We hear of it at first as a plague which infested armies and besieged towns; later as a disease which decimated the sailors of the navy and of the mercantile marine in the days when sailing vessels made long voyages and before refrigeration of foods was employed. In the Great War it again played a rôle; the report of the Mesopotamia Commission states that 7500 men were lost to the force in nineteen weeks as a result of scurvy; and it ravaged the British who were besieged at Kut-el-Amara. Since the latter part of the nineteenth century its main significance has rested upon the fact that it endangers the health of the artificially fed infant.

Incidence.—In some countries, for example in northern Russia and some parts of the tropics, scurvy is endemic. In the United States it is uncommon among adults, and is rarely represented in the mortality statistics. Neither age, sex, nor general vitality play a rôle in its etiology. It may develop in the young vigorous sailor or soldier, or in the aged and feeble, if the diet is deficient. It is impossible to estimate even approximately the frequency of occurrence of the mild undeveloped form which is brought about by a partial deficiency of the vitamin in the diet. The incidence among infants varies greatly in different localities. It is less common than it was some years ago when general pasteurization of milk was first required by cities and before it was realized that when milk is heated in this way the addition of an antiscorbutic food to the diet is necessary. It is met with among the infants of the rich as well as of the poor, since it may be caused by the repeated heating of the milk in order to insure sterility. Signs usually become manifest during the second half of the first year of life. After the second year it is exceptional, as by this time the scope of the diet has been enlarged. Latent and subacute cases occur, no doubt, far more frequently than is suspected or recognized. Among breast-fed infants scurvy is exceptionally rare—so exceptional that the diagnosis should be made with great hesitation.

Etiology.—Scurvy is usually caused by a diet which is deficient in fresh fruit and vegetables. Dried fruits have practically no protective power, and dried vegetables likewise have lost their antiscorbutic value. Much of the scurvy which occurred among the civil population of Europe during the recent war was due to placing mistaken reliance on such food. The potato is the mainstay against scurvy during the winter months. To such an extent is this true, that in some countries, for example, Norway and Ireland, whenever this crop has failed scurvy has manifested itself among the population. Cow's milk has mild antiscorbutic virtue, its original potency depending upon the vitamin content of the fodder of the cow. The power of heated milk to induce scurvy in infants is proportionate to the duration of the heating process and the exposure to oxidation rather than to the degree of heat.

The investigations of the past few years, especially those of Holst and Frölich, have taught us the fallacy of regarding fruits and vegetables as entities in respect to their antiscorbutic activity, and have demonstrated that they must be evaluated from a quantitative standpoint. A period of deprivation of about six months is necessary before scurvy becomes manifest. The time of its appearance depends on numerous secondary etiological factors, especially on individual susceptibility and the quantity of vitamin previously stored in the body.

There have been many theories as to the cause of the lesions of scurvy. Among these may be mentioned that which is based on a deficiency of potassium or of citric acid as well as the toxic and the bacterial theories. The latest, which appears well established, is the *vitamin theory*, which ascribes the disorder to the lack of a specific food factor, the antiscorbutic or *C* vitamin. This theory is derived from the data of animal experiments which have demonstrated that typical scurvy can be produced and cured at will by so regulating the diet that it is either deficient or well supplied with this vitamin. Whether this food factor is utilized by the body as a food or acts indirectly as a hormone is still unknown. Nor has it been

definitely determined whether the nutritional disorder is due entirely to lack of vitamin in the cells and tissues, or whether the deficiency leads to a secondary toxic state.

The *specific vitamin* is most abundant in fresh fruits and vegetables. Although it has never been isolated chemically in a pure state, it can be measured quantitatively by graded tests on animals, and much is known regarding its chemical attributes. It is soluble in water and in alcohol and it loses its potency on alkalinization, heating, drying, or aging. There has been a considerable change of opinion in regard to the effect of heat in the destruction of this vitamin. It was shown by Hess that heat in itself caused little destruction unless it was accompanied by oxidation; that, for example, milk may be dried or condensed and lose little of its potency provided it is not subjected to oxidation in the course of the process. A very small percentage of hydrogen peroxid destroys the vitamin in milk. Therefore, the suggestion of preserving breast milk by this means is to be deprecated. The fact that foods lose their antiscorbutic potency on aging—that stale milk is not as valuable a preventive as fresh milk, that vegetables fresh from the farm are superior to those which have been stored for long periods—is the result of gradual oxidation and destruction of the specific vitamin. A characteristic attribute of all the recognized vitamins is that they cannot be synthetized by animals, but are derived solely from the vegetable world. This is of marked practical significance in regard to prophylaxis against scurvy. It means that cow's milk may be rich or poor in vitamin according to the nature of the fodder, and that the quality of the milk which the baby obtains at the breast depends upon the food of its mother.

Morbid Anatomy.—Gross examination of a victim of scurvy generally discloses hemorrhages in the skin and in various organs and cavities. The heart is frequently enlarged and pneumonia may be found to have been the immediate cause of death. The long bones may show fractures, either united or healed with the formation of large calluses. Subperiosteal hemorrhages are very common, especially of the distal end of the femur or the tibia, but they may involve almost any bone and are of variable extent. Separation of the epiphyses is frequent in infants and young adults, and is most common in the femur at the knee-joint or at the head of the humerus. On sectioning the bones, the cortex is found to be exceedingly thin, and the marrow yellowish rather than red, with scattered foci of hemorrhage.

Microscopically the only characteristic lesions are those of the bones. There may be hemorrhages in the skin, muscles, lungs, serous membranes, gums, glandular organs, sheaths of the peripheral nerves, retina, etc. One of the peculiarities of the lesions of the bones is that they involve the end of the diaphysis or rather its junction with the cartilage. A section through a costochondral junction generally shows the following conditions: The juncture is not sharp and straight, but presents a wavy or irregular contour. The *Truemmerfeld area*, where the normal tissue is splintered and fragmented, may be seen. Here everything is in a state of disorder—trabeculæ of bone of various shapes and sizes lie scattered about; the cells are irregularly arranged and much distorted; there are signs of recent hemorrhage, and unrecognizable detritus is present. Higher magnification reveals few osteoblasts, a varying number of intact red cells, and more or less fibrin.

The cartilage is also abnormal; its cells are no longer in an orderly arrangement, but the proliferating columns have disappeared in the central portion. Below the Truemmerfeld area is the *Geruestmark or framework marrow,* another distinguishing feature of scurvy. It is composed of a loosely constructed fibrillar tissue on an apparently gelatinous groundwork of sparsely scattered cells and bony trabeculæ which are markedly thin and weak. Here and there are hemorrhages and bits of blood-pigment. The most typical site of hemorrhage, however, is beneath the periosteum which may be lined with newly formed bone or a deposit of lime salts. The walls of the blood-vessels are exceptionally thin. Recently lesions of the teeth have been described; especial interest is associated with such lesions, as they may have a causal relationship to some cases of dental caries.

Symptoms.—Although the identity of scurvy in the adult, young child, and infant is thoroughly established, there are sufficient differences between the symptoms of adult scurvy and those of Barlow's disease to render it necessary to consider them separately.

Adult Scurvy.—The earliest sign of scurvy in the adult is usually a change in the complexion. The color becomes sallow or muddy. The subject loses his accustomed vigor and complains of tiring quickly, and of breathlessness. There may be fleeting pains in the joints and limbs, especially in the legs, symptoms which are frequently attributed to rheumatism. Very soon the gums become sore, bleed readily, and are congested, spongy, and somewhat hemorrhagic at the edges. Absolute reliance must not, however, be placed on this sign for early diagnosis, since it sometimes does not appear until later. Careful examination at this stage discloses petechial spots or even larger ecchymoses on the body, more especially on the legs, at the site of the hair-follicles. Less frequently there is early bleeding from the nose, or the eyelid suddenly becomes swollen and purple, or the urine contains blood.

These signs progress steadily with varying degrees of rapidity. The complexion becomes more dingy and somewhat brownish, the weakness increases so that the slightest exertion causes breathlessness and palpitation, and the gums become spongy and even fungous. If there is infection of the gums and the teeth are carious, the breath is extremely foul, a sign long associated with scurvy. Later the teeth become loose and may fall out, and the alveolar process undergoes necrosis. A bloody diarrhea may supersede the constipation, which generally develops earlier in the disease. There are at this time hemorrhages into the muscles, especially into the calves of the legs, which give rise to the hard, brawny, tender swellings which have been termed "scurvy sclerosis." This is sometimes the earliest sign noted by the patient. Not infrequently subperiosteal hemorrhage produces exquisitely tender swellings, especially on the tibia or femur, or on the ramus of the lower jaw. Any wounds or ulcers assume a hemorrhagic aspect, the edges becoming bluish or livid and showing no tendency to heal.

At present the disease usually does not reach this stage, and rarely progresses further. If, however, the patient remains untreated, he becomes progressively weaker. The pains in the limbs render him helpless and an object of pity. Marked edema may ensue as the result of starvation, so that the legs become swollen, and the face even bloated. The gums swell to such an extent that they overlap and may even hide the teeth and protrude from the mouth as foul fungoid growths. Death is caused in various

ways; frequently sudden and fatal syncope occurs, or secondary pneumonia proves fatal.

Infantile Scurvy (*Barlow's Disease*).—The picture commonly suggested by the term *infantile scurvy* is that of the acute form of the disease. This is generally seen in a poorly nourished, pale infant with a peculiarly alert and worried expression. The child whimpers or cries out in terror when the bed is approached. Frequently the posture is characteristic—the infant lies quietly on its back with one thigh everted and flexed on the abdomen. Examination shows either that one or even both thighs are swollen and exquisitely tender, or that there is merely tenderness—the baby shrieking at the slightest pressure upon the lower end of the femur. If teeth are present, the adjacent gums are red, swollen, and bleed readily. This is the acute, florid type of manifestation of the disease.

The commoner form is *subacute infantile scurvy* which frequently is incorrectly interpreted. This usually affects children between six and twelve months of age. They may be fairly well nourished, but not gain weight satisfactorily, and are pale or sallow. The mother or nurse complains that the child is irritable and peevish and that the appetite is poor or capricious. The gums show a lividity or slight peridental hemorrhage. Attention may be called to the more or less definite tenderness of the lower end of the thigh. The urine may contain a trace of albumin and a few red blood-cells.

In addition to these manifestations are the latent disturbances referred to above, which can be diagnosed mainly by the fact that the malnutrition, lack of vigor, muddy color, poor appetite, etc., disappear at once when orange juice, tomato, potato, or other antiscorbutic food is administered in sufficient quantity.

Complications.—The complications of scurvy are, for the most part, the result of either hemorrhage or infection. One of the commonest complications is *proptosis* of the eyeball following hemorrhage into the orbit; this sign must be borne in mind, as it may occur before other local symptoms have rendered diagnosis obvious. *Hematuria* may occur, and there may be blood in the stools, severe bleeding from the nose, cerebral hemorrhage, or hemorrhage into the abdomen which may be difficult to interpret. Serous effusions develop at times in various parts of the body, especially in the pleural and pericardial cavities. *Edema* is not uncommon and may involve the face, legs, and scrotum. *Fever* frequently accompanies scurvy, generally of a low grade, the temperature ranging between 100° and 101° F. One of the most characteristic features of scurvy is that it lowers the resistance to infection. This likewise constitutes its greatest danger. The respiratory tract is particularly vulnerable, and pneumonia is the most common cause of death. Other secondary infections encountered are influenza, nasal diphtheria, furunculosis, torpid ulcers of the skin, pyelitis, otitis, adenitis (bubo) and gingival pyorrhea.

Diagnosis.—A correct and early diagnosis of scurvy is the more important, since there is a specific remedy and the disorder is not self-limited. When diagnosis is uncertain the most important aid is an exact knowledge of the previous diet and observation of the reaction of the patient to antiscorbutic treatment. The scurvy of adults and infants is very much alike. The main difference is to be found in the subjective symptoms in the adult—pains in various parts of the body—and the fact that the gums are frequently

the site of infection and ulceration as well as of hemorrhage. Time and again, in spite of urgent and repeated warnings, patients with scurvy are treated for *rheumatism*. Differentiation is not difficult. The diagnosis of rheumatism in infants indicates a lack of knowledge of pediatrics, for this disease hardly ever occurs in children under two years of age. In adults careful examination shows that the "rheumatic" pains and tenderness are not in the joints, but in the muscles and tendons. The calf muscles are frequently excessively tender, painful, and somewhat infiltrated. The gums are usually hemorrhagic, but since the pains may precede this sign, a diagnosis of scurvy cannot be ruled out because the gums are normal. One of the main points to be kept in mind in differentiating scurvy from rheumatism and all other diseases is that it may develop in any individual; most errors are due to the fact that its presence has not been suspected.

It is not always easy to differentiate scurvy from *purpura*, especially when pyorrhea and gingivitis are present. In either disease the gums may be hemorrhagic and swollen, and pains in the limbs may be complained of. Occasionally it is necessary to resort to the dietetic test. Inquiry into the previous diet, a history of previous attacks of purpura, the number and especially the large size of the subcutaneous hemorrhages, and, above all, the diminished number of blood-platelets, should render diagnosis possible. In scurvy there are almost always over 300,000 platelets per cubic centimeter of blood, whereas in purpura the count is reduced to less than 200,000.

In differentiating infantile scurvy from *"the pseudoparalysis" of congenital syphilis* it should be remembered that the luetic lesions almost always develop before the fifth month of life. A history of previous papular eruptions, the bilateral enlargement of the epitrochlear glands, and the Wassermann reaction should suffice to establish the correct diagnosis.

Besides these conditions, neuritis, hemorrhagic nephritis, calculus of the urinary tract, renal tumor, orbital tumor, appendicitis, peritonitis, pleurisy, and pneumonia have been confused with scurvy. Holt writes: "I have known 2 cases to be operated upon by eminent surgeons, once with the diagnosis of sarcoma, and once, of ostitis of both tibiæ. Not until the subperiosteal hemorrhages and epiphyseal separations were discovered was the nature of the trouble suspected."

Prognosis.—The outcome of scurvy as it is encountered in times of peace is generally favorable. There is a satisfactory specific remedy, so that if the diagnosis is made early and treatment is prompt, the patient recovers without permanent disability. The heart may be weakened by scurvy and its action be rapid for long periods after apparent cure. The chief danger of the disease is that it increases the susceptibility to infection, especially to pneumonia, which may lead to sudden collapse and death. Under proper treatment the local signs disappear quickly and the hemorrhages are absorbed. Fractures unite promptly. The urine becomes normal and gives no further evidence of renal damage. If treatment is not instituted death is caused by intercurrent infection, most often by pneumonia or enteritis.

Prophylaxis.—To avoid scurvy the diet must contain an adequate quantity of antiscorbutic foods, in other words, fresh fruits and fresh vegetables. Raw milk or raw meat suffice if taken in sufficient quantity. Among the fruits, lemons and oranges are the most valuable; among the vegetables, cabbage, tomatoes, and potatoes. The prevention of scurvy in adults is

not a problem in temperate zones in peace times, but it is at times difficult to prevent the development of the disease in infants. Every baby which is not nursed must receive a daily quota of antiscorbutic food in addition to cow's milk after the first month of life. At first 1 teaspoonful of orange juice is given (diluted with water and sugar if it is tart); this quantity is gradually increased until 1 tablespoonful is fed at three months of age. If tomato juice is chosen, these amounts should be doubled. Canned tomato (strained) serves the purpose as well as raw tomato juice and does not require cooking. No reliance should be placed on dried prunes or on beef juice, nor on small quantities—1 to 2 teaspoonfuls—of vegetables weak in antiscorbutic power, such as carrots or beets. This is especially true if the vegetables are old and have been cooked for long periods.

Treatment.—There is almost no form of treatment to which the patient's reaction is as prompt and striking as it is to the administration of an antiscorbutic diet. A magic result is seen frequently in twenty-four to forty-eight hours; and within a week, if the case is mild, all symptoms of scurvy may have disappeared. In the cure of scurvy the same dietetic remedies are employed as in its prevention. *Orange* or *lemon juice* is the sovereign remedy and should be given in as large amounts as possible. Drugs are of no avail whatsoever. The patient should be kept in bed, and exertion avoided on account of the danger of collapse. The *gums* may be treated with nitrate of silver or tincture of myrrh. If there is a *fracture* of the long bones with displacement, splints should be applied. Under no circumstances should *hemorrhagic effusions* in or about the joints be incised. The room should be airy, and the patient handled as little as possible so as to avoid discomfort and pain.

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RICKETS

Definition.—Rickets is a chronic nutritional disorder of infants and children which is manifested particularly by alterations of the bones, more especially of the epiphyseal ends.

History.—A remarkable feature of rickets is its sudden appearance (or marked increase in incidence) in the seventeenth century. This led to the report of Glisson and the publication of his classical treatise in 1660. During the past few years interest in the disease has been revived by investigation of the vitamins and by the fact that it is possible to produce rickets in animals and study it by the experimental method.

Incidence.—Rickets occurs with greatest intensity in the temperate zones and is mild or absent in the tropics. It is particularly a disorder of cities and of the large industrial centers, although it is by no means absent in the rural districts. Thomson is of the opinion that more than 50 per cent. of the infants of Edinburgh, London, Glasgow, and Manchester show unmistakable signs of the disease. The same figure probably holds true for New York.

There is a marked seasonal augmentation and diminution in the incidence, as was noted by Kassowitz many years ago, and demonstrated by the necropsy reports of Schmorl. Rickets begins to increase in the fall, becomes more marked in the winter, and reaches its peak in March; the incidence then steadily declines, and new cases rarely develop after June. As is well known, Italian and negro babies in our large cities are especially prone to develop this disorder. Premature infants are notably predisposed to rickets, probably on account of their exceptionally rapid rate of growth. To a less extent this is true of twins. The disease is encountered most often in children between six and eighteen months old. It does occur earlier, but is not congenital. There is a late form called *"rachitis tarda"* which appears about the time of puberty, but is very rare except under conditions of such extreme privation as occurred in the Central Empires during the World War.

Etiology.—Rickets has been ascribed to almost every influence which is known to be harmful to human beings—to defective hygiene, improper diet, intestinal toxins, bacterial infections, syphilis, derangement of the secretion of the endocrine glands, hereditary factors, etc. It is probable that there is a prenatal factor in its etiology, and that the diet and regimen of the mother affects the child in some way, but this is of secondary importance when compared with postnatal factors. The disorder is not transmitted by the germ plasm. Until recently there was a sharp difference of opinion as to whether rickets was the result of improper diet or faulty hygiene. Today it is known that both factors are involved. There is general agreement that bottle-fed babies develop rickets with far greater frequency than those which are breast-fed. It should not, however, be thought that rickets is rare in the nursing infant; it is not uncommonly found when careful methods of diagnosis are employed. The purity of the cow's milk plays no rôle in the etiology; that rickets may develop even when the best milk is given, is frequently seen among the infants of the well-to-do. In many cases rickets is associated with a diet poor in fat, composed chiefly of condensed milk or of the various proprietary cereal foods. There seems to be little real connection between the two, however, and it is probable that the rickets-producing effect of carbohydrate is largely due to the fact that this form of food leads to rapid growth. Other etiological factors being constant, the occurrence of rickets depends largely on rate of growth. In an institution for children the writer found that about 75 per cent. of the cases developed among the well nourished and only 25 per cent. among the poorly nourished infants. This incidence is quite contrary to that of infantile scurvy.

The greatest recent advance in our knowledge of rickets is an understanding of the precise nature of the hygienic factor. This has been shown to be *sunlight* rather than fresh air, exercise, cleanliness, etc. Infants do not develop rickets in the summer on account of the protective effect of

the sun's rays. This is due to the ultraviolet radiations and not to the visible rays. These radiations have very slight power of penetration, and are absolutely filtered out by window glass, so that a baby can receive none of their protective properties if it is kept in a room with the windows closed, notwithstanding the fact that it is in a flood of light. The effect of the sun's rays is probably due to an activation of the cholesterol in the superficial layers of the skin.

Syphilis plays little or no rôle in the etiology of rickets. There is no clinical or experimental evidence in favor of the bacterial theory or an involvement of the endocrine glands.

Metabolism.—The chemical nature of the dietary defect which leads to rickets is as yet unknown. Evidently it is not a simple deficiency of calcium or of phosphorus, for, if it were, rickets would occur more often in children living on human milk than in those receiving cow's milk. As the result of animal experiments Mellanby suggested that a vitamin is lacking, the so-called *vitamin A* (fat-soluble vitamin), or one closely associated with it. The time is not ripe to appraise accurately the rôle of vitamins in the etiology of rickets.

One of the main advances in our knowledge of the metabolism during rickets is the realization of the importance of *phosphorus;* until recently attention had been focused on calcium. The inorganic phosphorus content of the blood is diminished, whereas its calcium content is approximately normal. The ratio of these metals is, however, normal in the bones, even in severe cases, although the total amount of ash is diminished. It has not been determined whether the lack of calcium and phosphorus is due to deficient absorption or to deficient retention. Recent investigations seem to point to abnormal absorption in the intestinal tract, due to a faulty chemical reaction and an unfavorable interrelationship of the salts of calcium and phosphorus.

Schabad showed some years ago that *cod-liver oil*, when administered to rachitic individuals, is able to change a negative to a positive calcium balance. Sunlight or artificial ultraviolet radiation brings about a similar result and raises the inorganic phosphate of the blood to normal.

Morbid Anatomy.—Although rickets should be regarded as a systemic disorder, our knowledge of its pathology is confined almost entirely to the bony structure. The distinguishing characteristic is that the bone which is newly laid down is not of normal composition, but is either an uncalcified or an improperly calcified tissue; and, furthermore, is superabundant. Gross examination shows an involvement of the cranium, which may be the seat of atrophic as well as of hypertrophic changes; there may be evidence of craniotabes as well as bossing of the parietal bones. The thorax is frequently deformed and enlargements are evident at the costochondral junctions, the so-called "rachitic rosary." The shafts of the bones are frequently bent, especially those of the lower extremities. On longitudinal section the distinctive feature is the irregularity of the zone of calcification which runs zigzag across the epiphysis.

The chief result of the rachitic process is the production of *abnormally soft bone.* The significant feature as shown by Pommer is the development of an excess of osteoid tissue which is imperfectly calcified. Normal bone has a narrow border of osteoid material surrounding the trabeculæ of spongiosa; in rickets the osteoid may in extreme instances almost fill the

marrow cavity. That which springs from the periosteum may form irregular masses—the periosteal callus—or be laid down in layers, or as small hard osteophytes. The layer of osteoid substance is adjacent to the cartilaginous layer and of varying width. It contains islands of uncalcified cartilage which may be sufficiently large to be distinguished with the naked eye. The marrow itself is highly vascular—a condition which Kassowitz interpreted as inflammatory, and which he regarded as the primary lesion of rickets.

The disturbance in *endochondral ossification* is especially marked, and leads to a confusion of the various layers. The cartilaginous zone is markedly increased and may be many times its normal width. When healing takes place a thin, more or less irregular, transverse stripe is formed within the cartilage. This may be apparent macroscopically as a yellowish-white line, and when seen in roentgenographs is significant of healing.

Symptoms.—Like infantile scurvy and other abnormal nutritional states, rickets is generally so incompletely developed that it does not attract attention. The earliest symptoms are restlessness, irritability, and head sweating—signs which are suggestive rather than indicative. Soon thereafter the *costochondral junctions* ("the rachitic rosary") become enlarged. This is the most reliable early sign of rickets. The head becomes somewhat square in shape, the fontanel is too widely open, and areas of softness may be felt along the lower part of the occipitoparietal suture. The *epiphyses* at the wrist may be enlarged and radiographs disclose changes in the ulna which are typical of rickets. Chemical examination of the *blood* reveals a deficiency of inorganic phosphates. All these signs are not present in every case. In an infant which seems to be thriving and is of average weight and healthy appearance, such slight divergencies from the normal may readily be overlooked unless a routine search is made.

The well-developed or advanced stages are evident at a glance. The *head* is square; the *thorax* deformed, with not only two lateral rows of visibly enlarged costochondral junctions, but a groove traversing its lower part (Harrison's groove) or deep furrows compressing and deforming it on either side. The *abdomen* is large and protuberant—the well-known "pot-belly"; the stools are costive rather than loose. The *legs* are bowed or knock-kneed and the ligaments lax. The infant may no longer be well nourished, for the extreme stages are associated not only with retardation of the gain in weight but also of the increase in length.

Muscular weakness is frequent. The muscles of the legs may be undeveloped and soft, or large and flabby. Those of the back may be unable to support the trunk when the child is placed in the sitting posture. The abdominal muscles frequently show evidence of weakness; diastasis of the recti muscles, umbilical hernia, and bulging of the lateral walls are common. The weakness of the limbs may be so extreme that the infant is hardly able to move them and appears paralyzed.

A great deal of attention has been devoted to the presence of *craniotabes*. This sign should not be confused with the softening of the skull which is so frequently noted in the newborn. On account of the difficulty of differentiating between this simple osteoporosis and rachitic craniotabes this sign has little significance until after the fourth or fifth month of life.

It is true that rickets may lead to *tardy dentition*, but there are so many other causes of delayed teething that little weight should be attached

to this symptom. The closely related question of the effect of rickets on the quality of the deciduous and the permanent teeth, in other words, of its rôle in the development of dental caries, cannot be answered at present. It seems certain, however, that it is not the main etiological factor.

Spinal curvature is another abnormality of the bone brought about by rickets. This deformity is of little aid in establishing an early diagnosis, but may constitute an important residual sign of rickets. Kyphosis is the common form of curvature, and differs from tuberculous kyphosis in that it is less angular, not tender, and readily reducible on traction. Any of the bones in the body may be affected by rickets. The upper extremities are generally less involved than the lower. The clavicle is frequently bent and shows permanent signs of an infraction at the junction of its outer third and inner two-thirds. Fractures of the long bones are not infrequent and may be quite overlooked until they are demonstrated accidentally by the Roentgen ray. The pelvis may be deformed and assume the typical flat or rachitic shape which causes difficulty in parturition in adult life.

The *radiographic picture* is typical. The characteristic changes first occur at the lower epiphyses of the ulna and femur. The lower end becomes broadened and its inferior surface no longer sharp and straight, but concave and irregular. This surface may appear as if bordered by an uneven fringe. The shafts of the bones are reticular and less well calcified. Development of the carpal centers may or may not be delayed.

It has been found recently that there is a characteristic chemical alteration of the *blood* during rickets. The percentage of inorganic phosphate is diminished. The normal content of the blood in infants is about 4 to 4.5 mgm. per 100 c.c. of plasma. In active rickets the percentage falls to 3.0 or 3.5 per cent., or even lower in the severe forms. This observation is in harmony with that of Hess and Lundagen, that there is a seasonal variation in the inorganic phosphate content of the blood of infants—an ebb in the winter and early spring and a flood in the summer. This variation runs parallel with the seasonal curve of the incidence of rickets. The calcium content is normal or but slightly diminished. There is often a moderate secondary anemia with some reduction of hemoglobin and of red cells.

Complications.—As is well known, *tetany* is frequently associated with rickets and has a similar seasonal incidence. It is characterized by hyperirritability of the nervous system which leads to convulsions and to increased mechanical and electrical excitability of the nerves. There is also a characteristic diminution of the calcium content of the blood. It has been suggested by Parks and his associates that tetany should be regarded as a form of rickets which involves the calcium rather than the phosphorus metabolism. Like rickets, it may be cured by ultraviolet irradiation or cod-liver oil.

It is an observation of long standing that rachitic children are predisposed to *infections of the respiratory tract;* in fact, this is one of the main dangers of the disorder. Bronchitis and pneumonia are frequent complications. Italian infants in the large cities are especially susceptible to both rickets and the respiratory diseases.

There is a form of anemia termed *"von Jaksch anemia"* which is frequently associated with rickets, but must not be considered as the result of

rickets. It is accompanied by typical changes in the blood and a marked enlargement of the spleen. The lymph-nodes also are generally swollen.

A mild degree of *hydrocephalus* is frequently developed during rickets. It is difficult to differentiate this rachitic type from the non-rachitic, except by a consideration of all the concomitant signs. Accompanying the enlargement there is the usual dilatation of the superficial cranial vessels and of the fontanel. The hydrocephalus is almost always of mild grade.

Relationship has been suggested between rickets and *syphilis*, *tuberculosis*, *malaria*, and *epilepsy*, but has not been established clinically or experimentally. Nor is there any relationship between rickets and *scurvy*.

Diagnosis.—For various reasons rickets is more often overlooked than recognized. First among the sins of omission is the failure to examine patients for rickets—the tendency to ignore its existence unless the signs are self-evident. Furthermore, the technic of examination is frequently faulty; in looking for beading of the ribs the thorax is palpated too far anteriorly or posteriorly; in testing for craniotabes only limited areas of the cranium are palpated. Furthermore, the signs and symptoms of the early stage are obscure, as in all nutritional disorders.

Of the direct clinical signs the greatest stress should be laid on *beading of the ribs*. A rosary of moderate degree is diagnostic of rickets in a baby over three months of age. Just what degree the beading must attain to be of diagnostic value can be learned only by experience. *Enlargement of the epiphyses* is a later and far less reliable sign. *Craniotabes* is of value according to the age of the baby; it is of little or no value in infants under three months, but may always be considered of rachitic origin after six months of age. The radiograph is of great aid in diagnosis. It should be borne in mind, however, that radiographic changes do not appear early and that the rachitic process must have been developing for some months before the lesions can be demonstrated by the Roentgen ray. The diminution in the *inorganic phosphate of the blood* is a very valuable diagnostic sign, especially where the "rosary" is of uncertain degree and the radiograph negative. It is frequently the earliest manifestation of rickets.

Such symptoms as delayed eruption of the teeth, pot-belly, and delay in learning to stand or walk have little diagnostic value and have been too greatly stressed. Later signs, such as deformity of the thorax or of the long bones, require only passing mention. Whether bowed legs are always due to rickets is questionable. Certainly a "chicken-breast" or a funnel-shaped chest may develop in non-rachitic children.

In the differential diagnosis the main diseases to be thought of are *infantile scurvy* and congenital syphilis. The former is at times confused with rickets, and may even be treated as rickets. The scorbutic baby is generally poorly nourished, unhappy, has a capricious appetite, and, above all, is tender to the touch. When its thorax or the lower ends of the thighs are pressed it shows distinct signs of pain. Rickets does not lead to bone-tenderness. Scurvy induces hemorrhage of the gums, petechiæ in the skin, and the appearance of red blood-cells in the urine. The inorganic phosphate of the blood is normal in scurvy; and the radiogram is normal or shows the "white line" of Fraenkel at the epiphyses. The fact that beading of the ribs may occur in either disorder has furthered the confusion.

Fournier believed that rickets was due to *syphilis*, and Marfan accords

this infection an important etiological rôle. In both diseases the head may be enlarged with frontal bosses, the long bones curved, craniotabes present, and the stature dwarfed. The Wassermann reaction, the facies, the history of an eruption, the bilateral enlargement of the epitrochlear glands, the enlarged and hard spleen of syphilis should serve as means of differentiation. The radiographic picture may be confusing. The inorganic phosphate content of the blood is not diminished in congenital syphilis.

Prognosis.—The prognosis is generally very favorable. The majority of cases are very mild, so mild, indeed, that many pass unrecognized and leave no local deformity or systemic disturbance. Recovery comes spontaneously with the fortuitous advent of spring or summer, of the decrease in rate of growth, and the administration of a varied diet. Bowed legs, beading of the ribs, enlarged epiphyses gradually disappear and the bones regain their normal contour in most cases, although not in all. These signs may, however, persist, as well as the square head, the deformed chest, the scoliosis, kyphosis, and flat-foot. The pelvic deformity is the most important, as it may lead to varying degrees of dystocia. In severe instances permanent stunting of the growth may lead to dwarfism; in such cases the diet has generally been inadequate in several respects.

Prophylaxis.—Rickets is unique in that it is the only disorder for which we possess two specific therapeutic agents—cod-liver oil and ultraviolet irradiation. One of the best prophylactic measures is maternal nursing or administration of human milk. This is, however, by no means a safeguard even if the mother's diet has been adequate during pregnancy and lactation. In the writer's experience, a food which has proved of protective value is yolk of egg. Infants one to two months of age are given one-half of the yolk of a raw egg mixed with the daily formula. At three months an entire yolk may be given.

Hygiene plays an important rôle in prophylaxis. *Sunlight* is particularly necessary; fresh air and cleanliness to a far less extent. Infants should be out of doors as much as possible and not shielded from the rays of the sun; their arms and legs may be exposed while their bodies are protected against the cold. In view of the prevalence of rickets, it seems advisable to give every baby *cod-liver oil* as a routine practice, on the same principle that we give fruit juices to prevent scurvy. Cod-liver oil is an excellent specific and should be administered in small doses from October to May. Five drops of the pure refined oil should be given three times a day at the age of one month, or 15 drops mixed with the day's total feeding. The dosage should be increased until the baby receives $1\frac{1}{2}$ teaspoonfuls daily at three months. Few babies do not tolerate cod-liver oil. Standard emulsions may be used, but the actual dosage of oil must not be thereby decreased. Phosphorus may be given, but should not be considered a substitute for the oil.

The other specific for rickets is the *ultraviolet radiation* furnished by sunlight, the mercury vapor lamp (air cooled), carbon arc lamp, etc. This agent is of great value in the winter months and may be employed with cod-liver oil or as a substitute when the oil is not well tolerated. The mercury vapor lamp is placed at a distance of 3 feet from the baby and irradiations given every other day in increasing doses, from three to twenty minutes. The skin should become tanned, but not blistered; different parts of the baby are selected for successive treatments. The carbon arc

lamp accomplishes equally good results. Ultraviolet therapy is likewise of specific value in the treatment of tetany.

It has been recently shown by the writer and by Steenbock that various foods and sterols—for example, cholesterol and ergosterol—develop antirachitic properties after having been subjected to ultraviolet radiations. It is quite possible that this phenomenon will be made use of in the prophylaxis of rickets. For example, dry milk or yeast which had been endowed with this property might be used in this connection.

Treatment.—For the cure of rickets the same measures are employed as for prophylaxis. An infant six months or more of age should receive 3 teaspoonfuls of cod-liver oil daily. In the case of premature babies it is often of value to combine oil and irradiation therapy.

In addition to these specific measures *massage* is of value to increase the turgor of the muscles. *Iron* is necessary to combat the anemia which may develop, and orthopedic or surgical procedures to correct deformities. It is surprising how often marked bowing of the legs rights itself spontaneously as the child grows and develops.

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DISEASES OF METABOLISM

GOUT

(*Podagra*)

Definition.—Gout is an inflammation of the joints, either acute or chronic, attended by the deposition of sodium urate crystals in or about the affected joints. The disease is due to a disturbance of the uric acid metabolism. In chronic cases there is often a deposition of sodium urate in the subcutaneous tissues, most commonly at the margin of the ear, in nodules of varying size which are termed *tophi*. The blood in gout, even between attacks, contains an abnormal amount of uric acid. The output of uric acid in the urine is usually less than normal.

History.—Syndenham (1624–1689) was the first to distinguish gout sharply from the other forms of arthritis. His clinical description of the symptoms and signs of acute gout is a masterpiece and upon it most subsequent accounts have been based. Knowledge of the nature of gout began with the discovery of uric acid by the chemist Scheele in 1776. Wollaston in 1787 proved that the "chalk stones" that form in gouty subjects are composed of uric acid. Alfred Garrod made pioneer chemical studies in gout and was the first to demonstrate an excess of uric acid in the blood in gout. He also recognized that the urine contains less uric acid than in health. Folin in 1913 developed a clinical method for estimating the uric acid in the blood. This has been improved and made more accurate by Benedict and by Folin.

Etiology.—Heredity.—In many instances, possibly in all cases of gout, the instability or abnormal tendency of purin metabolism is inborn. Llewellyn, an English authority on this disease, believes that gout is always an hereditary disorder, but one which may remain latent throughout life. In America the hereditary factor in gout is less apparent than in England. Among the patients studied in the wards of the Peter Bent Brigham Hospital of Boston in the past ten years, not one gave a family history of gout, while the statistics of English physicians show that 50 to 75 per cent. of their patients came from gouty stock.

Alcohol is a potent factor in the production of gout. This has been recognized by all students of the disease since Greek and Roman times. Garrod thought that if fermented liquors had never been taken as a beverage there would have been no gout. Wines, porter, beer, and ale favor the development of gout more than do distilled liquors. Among 44 patients with gout in the Brigham Hospital series, 17, or 39 per cent., admitted they had been heavy drinkers, 13 claimed they took alcohol in moderation, 11 did not use it, and the use of alcohol by the remaining 2 is not stated.

Overeating.—There is a direct relation between gout and an excessive consumption of food, especially protein. Gouty patients are, as a rule, overweight. They are often large meat eaters.

Lead.—There is a definite association between lead poisoning and gout in countries in which the latent tendency to gout is strong. In England, the two conditions frequently co-exist; in America, on the other hand, gout is rarely found in patients with lead poisoning.

Sex.—Gout is rare in women, as may be seen in all careful statistical

studies. There were only 4 women in the Brigham Hospital series, and in 2 of these the diagnosis was doubtful. The author has seen only one case of tophaceous gout in females, and no tophi were found in the 4 cases at the Brigham Hospital.

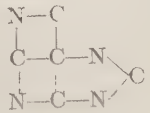
Distribution.—There is a marked variation in the incidence of gout in different countries, and at different periods in the same country. It was very common in Rome 2000 years ago, but is rare at the present time in Italy and in other Mediterranean lands. England has been its home for centuries. The frequency and severity of the disease has lessened there during the last hundred years. Allbutt, in his recent monograph, says that acute gout has become a rarity in hospital practice in England. Prior to the World War the incidence of gout was increasing in Germany, but attacks ceased during the food shortage. In America the disease is, without doubt, much more rare than in England and Germany.

A careful search for gout has been made by Christian and his associates since the Peter Bent Brigham Hospital opened in 1913. Out of a total of 24,766 admissions to the medical wards up to November 1, 1924, there were only 44 cases of gout. As some patients were admitted more than once the total number of admissions was 55. This is only 0.2 per cent. of the total number of medical admissions. At St. Bartholomew's Hospital, in London, the incidence was 0.37 per cent. Statistics published from the Johns Hopkins and Cook County Hospitals indicate that gout is more common in Baltimore and Chicago than in Boston. Eleven of the Brigham Hospital patients, or 25 per cent. of the whole number, were born in Europe; 5 of these were Germans. This suggests that a considerable portion of the gout in America may be imported.

Age.—Gout rarely develops in individuals less than thirty years of age. Thirteen of the 44 cases in the Brigham Hospital series began in the fourth decade. In only 1 case did the first attack occur before the age of twenty. The youngest patient at the time of admission to the hospital was twenty-seven. Tophi are rarely found before the age of forty. The youngest patient seen by the writer with a tophus in the ear was a soldier at Camp Devens. He was about twenty-eight years old.

Uric Acid Metabolism.—The chief source of uric acid is the nuclei of the cells of the animal body and the nuclei of the animal and plant cells taken as food. All cell nuclei contain a complex substance called nucleic acid, which, in the cell, is united with protein. This combined substance is called *nucleoprotein*. The protein portion is digested by the gastric and pancreatic juices. Nucleic acid freed from protein is split by the secretion of the small intestine into the four mononucleotids of which it is composed. The adenin and guanin nucleotids present in every molecule of nucleic acid are set free, and are probably absorbed unchanged from the intestine. In the blood Jackson found about 25 mg. of adenin nucleotid per 100 c.c. of blood. This was present only in the cells.

Uric acid is a purin substance which contains the so-called purin framework. This is a combination of 5 carbon and 4 nitrogen atoms united to form the chemical structure shown in the diagram:



The word purin was coined from purum uricum. The simplest member of the purin series is the hydrogen compound, purin $C_5H_4N_4$. By the addition of one oxygen atom to purin there is formed hypoxanthin $C_5H_4N_4O$. Xanthin (di-oxypurin) contains two atoms of oxygen, $C_5H_4N_4O_2$. Uric acid is tri-oxypurin, $C_5H_4N_4O_3$. The replacement of an atom of hydrogen in purin by an amino group (NH_2) forms adenin, which is aminopurin. The addition to this of an oxygen atom gives rise to guanin, which is amino-oxypurin.

There are specific ferments in the body which convert adenin and guanin nucleotids into simpler bodies called nucleosids which contain the purin body united to a sugar. De-aminizing ferments change adenin and guanin into hypoxathnin and xanthin. Oxidizing ferments can form uric acid from hypoxanthin and xanthin. All the lower animals except the apes have a ferment uricase, which breaks uric acid down into allantoin. In man and in the chimpanzee there is no uricase, and it has been generally held until recently that uric acid is an end-product in the human organism. Recent investigations, however, especially those of Folin, Berglund, and Derick, make it highly probable that uric acid is destroyed in man. Allantoin is abundant in the urine of dogs and in other animals that have uricase in the liver, but is found only in traces in the urine of man. Uric acid can by oxidation yield allantoin, but it is possible that other substances besides allantoin may be produced by oxidation of uric acid within the body.

Uric acid is rapidly destroyed when injected into the circulation of a dog. This destruction takes place in the blood, but it ceases the instant the blood is withdrawn from the body. An unknown oxidizing agent is apparently contributed by some tissue of the body and is used as rapidly as it enters the blood. This active destruction of uric acid cannot well be ascribed to an enzyme (Folin, Berglund, and Derick).

Folin and his co-workers have also shown that uric acid introduced into the blood-stream is taken up in considerable amount by the kidneys. It does not apparently pass from the blood to any other organ or tissue. After the level of uric acid in the blood is lowered by its destruction therein, a portion of the uric acid passes back from the kidney to the blood.

The theory that uric acid is destroyed in man as well as in lower animals is strengthened by the result of injecting uric acid into the blood. It has been repeatedly shown that when uric acid is thus introduced only a portion, usually about 50 per cent., is excreted in the urine; yet it is known to disappear for the most part from the blood within a few minutes. If uric acid does not pass from the blood to the muscles and tissues, the most probable explanation of the rapid disappearance of injected uric acid must be found in its destruction in the blood. When purin foods are fed, only 25 to 50 per cent. of the purin appears in the urine as uric acid. Probably a large part of the remainder is absorbed from the intestine and converted into uric acid, but instead of being excreted it is destroyed.

The uric acid in the urine comes partly from purins in the food, and is called *exogenous uric acid*. The remainder, which originates in the body itself, is the *endogenous uric acid*. This is probably formed in large part from the degeneration or the activity of the nuclei of the cells of the body.

The amount of uric acid excreted daily by an individual living on a purin-free diet—endogenous uric acid—is fairly constant in a single individual, but varies in different individuals. In normal persons it is rarely

less than 0.3 gm. or more than 0.6 gm. Experiments show that the human kidney can excrete uric acid far less readily than the kidney of the dog or the goat. The amount of uric acid in the blood of normal individuals as determined by the new methods of Folin and Benedict is usually between 3.00 and 4.5 mgm. per 100 c.c. of blood.

Uric Acid in the Blood and Urine of Gouty Patients.—The quantity of uric acid in the blood of gouty patients is almost always greater than normal. Higher values are obtained with the modern method of analysis than with the original Folin procedure. The amount of uric acid in the majority of cases ranges between 5 and 9 mgm. when the diet is poor in purin, and a little higher when it contains the usual amount of purin.

The endogenous uric acid output in gout is usually low. From data published in the literature the writer has found that the average daily excretion of 20 gouty patients was 0.25 gm. In some cases very low figures have been obtained, especially when gout is associated with chronic lead poisoning. In one of the author's cases which was complicated by severe chronic nephritis the output of uric acid in one day fell to 0.03 gm. Probably about 5 per cent. of the total number of patients with gout have a uric acid output which is either a high normal or supernormal.

In gout the purin contained in food is excreted less readily than in health. McClure and Pratt collected 50 observations from the literature. In 32 of these, 20 per cent. or less of the purin-nitrogen of the food was excreted as uric acid nitrogen. Brugsch and Schittenhelm have claimed that after an intake of food rich in purin a delayed excretion of uric acid is characteristic of gout. McClure and Pratt, however, were unable to confirm this statement. In 52 experiments on non-gouty, arthritic patients the exogenous uric acid output was completed within five days in 79 per cent. of the subjects, while in 46 experiments on gouty individuals the excretion of the purin ended within five days in 90 per cent.

Morbid Anatomy.—In the acute attacks there is engorgement of the veins and edema of the tissues about the affected joints. There may be exudation of fluid into the joint, but rarely of sufficient amount to be detected on clinical examination except when the knee is involved. The characteristic feature of acute gouty inflammation is the deposition of sodium urate crystals. These form only in situations where the circulation is normally poor. According to the best authorities sodium urate is deposited only in necrotic tissue. The urates are most commonly found in the cartilage of the joint. The sodium urate deposits are opaque and white, and give to the cartilage the appearance of being spotted with white paint. To the naked eye this coating appears to be on the surface, but it is always below the superficial lamina of the cartilage, and hence cannot be wiped off. Occasionally sodium urate is deposited in the synovial fringes or in the ligaments or other fibrous structures about the joint. The deposit is also found at times in the ends of the bone near the cartilage. It may occupy areas from which the osseous tissue has disappeared. Munk has recently studied the occurrence of sodium urate in bones. He finds that the changes which destroy the joints begin, as a rule, in the bone-marrow and are fibrous and osteomyelitic in nature. Sodium monourate may also be deposited in structures which are not the seat of acute gouty attacks. The most frequent location is the helix of the ear, but they are also found in the subcutaneous tissues elsewhere, most commonly in those of the hands and feet.

These are called tophi. The overlying skin often becomes thin and eroded so that the contents of the tophi are discharged. The material that exudes looks like a mixture of chalk and water. The contents of a fresh tophus are soft, but the material in an old one may be hard.

In chronic gout slight hypertrophic changes in the bones are common. The margins of the cartilages become thickened (enchondrosis). Ankylosis and dislocation of the joints are rare. Great deformity may result from the formation of tophi, especially in the hands.

There is a rare condition called *calcium gout* in which deposits of calcium phosphate and carbonate occur. This bears no relation to uric acid gout, but the inflammation about the calcium deposits may simulate that of true gout. The nodules may break through the skin and discharge a soft material macroscopically similar to the urates.

Symptoms.—Acute Gout.—An attack of acute gout usually comes on at night. The subject is awakened by pain in one of the feet. The metatarsophalangeal joint of the big toe is affected in the vast majority of cases, but sometimes the heel, ankle, or instep are involved. The pain, which is at first moderate, increases in intensity. It is described as grinding and crushing in nature, or as an intense burning such as might be caused by thrusting a red-hot iron into the joint. The weight of the bedclothes increases the suffering. Any vibration of the bed, such as may be induced by walking about the room, increases the distress. Toward morning the pain abates, and the patient falls asleep. On awaking he finds the joint swollen and the veins about it engorged. For a few nights the pain continues to return, but rarely in its original intensity. After several days the other big toe becomes inflamed and the pain and swelling lessen in the joint first involved.

A *joint* which is the seat of acute gout is greatly swollen and exquisitely tender. The *skin* is of a deep red color, tense, and shiny. The distention of the *veins* is striking. When the tenderness lessens the skin pits on pressure. As the swelling subsides the cuticle peels and there is often local itching.

The *fever* during a fit of gout is of moderate grade and there is usually a slight leukocytosis. In individual cases the symptoms vary somewhat. Instead of passing from one big toe to the other, the inflammation may involve the knee or some other joint. In many instances the patient has no premonition of an attack and goes to bed in the best of health. There may, however, be preliminary symptoms, such as flatulence, indigestion, and a capricious appetite. Predisposing causes of a gouty paroxysm are ingestion of meat rich in purins, overeating, indulgence in alcohol, lack of exercise, and slight injury to a joint, especially to that of the big toe. The average initial attack lasts for a week to ten days. Recovery is complete. The patient often feels remarkably well after an attack.

A *second seizure* follows the first after an interval of months or years. The average interval is not over a year. Other attacks follow at shorter intervals.

Chronic Gout.—In chronic gout, which often follows repeated attacks of acute gout, there is persistent discomfort and disability without intervals of freedom. The joints, especially those of the hands, are usually deformed. Tophi are more common in chronic than in acute gout and are often found on the feet and hands as well as on the ears. Tophi about the joints may interfere with free motion, most often of the fingers or wrists. Swelling

of the olecranon and prepatellar bursæ is common. The walls of the bursæ become thickened and their sac contains sodium urate. In severe cases there may be great crippling because of the involvement of many joints. One of Pratt's patients had gouty inflammation of the feet, ankles, knees, hands, wrists, elbows, and hips.

Polyarticular gout is rare. It differs from acute gout in that (1) many joints are inflamed, sometimes in succession, sometimes simultaneously; (2) the duration of the attacks is much longer, often months instead of days; (3) the initial attack less often involves the big toe. The *fever* may persist for weeks, and is apt to be higher than in acute gout, but lower than in rheumatic fever involving several joints. Sometimes acute polyarticular gout is afebrile. There may be a considerable leukocytosis. The condition is often mistaken for rheumatic fever.

Complications.—*Arteriosclerosis* develops early in gouty subjects. The arteries about the joints which are the seat of chronic gouty inflammation become sclerotic. There is often *hypertonia*. Hypertrophy and dilatation of the *left ventricle* are frequently present. *Chronic nephritis* of mild degree is common. The phenolsulphonephthalein excretion often varies between 30 and 50 per cent., and the non-protein nitrogen of the blood between 40 and 50 mgm. per 100 c.c. of blood. In Europe *diabetes* and gout are often associated, but rarely in this country. There was no glycosuria in any of the cases in the Brigham Hospital series.

Diagnosis.—The one pathognomonic sign of gout is the presence of tophi. Most careful search should be made for them in every case of suspected gout and in every case of polyarticular arthritis. Tophi are most commonly found on the ears, where their size varies from that of a pin-head to that of a pea. They are usually situated on the helix near its outer margin. They are yellow or white in color. Their identification is not complete unless the characteristic long needle-shaped crystals of sodium urate can be seen under the microscope. These crystals are composed of sodium monourate, not of the biurate, as is often stated in text-books. The elbows and knees should be carefully inspected for thickening of the olecranon and prepatellar bursæ. Chronic inflammation of these structures must be very rare in any condition except gouty arthritis. The author never saw it except in gout. Soft swellings, one or more centimeters in size, on the fingers, the back of the hands, the dorsal surface of the feet, and elsewhere, may be due to the settling of sodium urate in necrotic tissue. If tophi are not present on the ear, one of these nodules should be aspirated or incised in order to determine whether the characteristic crystals are present. If a thorough hunt is made tophi can be found in a large percentage of the cases of long-standing gout. They were present in 26 (59 per cent.) of the 44 cases at the Brigham Hospital, in which a diagnosis of gout was made. Some of the cases in which they were absent were probably not gout.

Acute inflammation of the metatarsophalangeal joints of the big toe is usually but not invariably due to gout. The writer has seen it in acute rheumatic fever, in hallux valgus, and in infectious arthritis. In women, mild podagra may occur without any increase of uric acid content of the blood and without the formation of tophi. The author has records of 4 such cases, but in no instance was he convinced that the condition was one of genuine gout.

Determination of the *amount of uric acid in the blood* is of considerable

value in diagnosis if nephritis can be excluded. The presence of 5 mgm. or more of uric acid per 100 c.c. of blood and a low non-protein nitrogen content is strongly suggestive of gout.

Radiograms of the hands and feet are of slight aid in diagnosis. Clear circular areas with sharp borders in the epiphysis of the bones were formerly thought characteristic of gout. They are common, however, in other forms of chronic arthritis, and are due to atrophy of the bony tissue. If the clear spaces are large, that is 5 mm. or more in size, they are indicative of gout.

A study of the *urine*, even when the patient is living on a purin-free diet, does not yield conclusive results. In gout the endogenous output of uric acid is usually low, *i. e.*, 0.3 to 0.4 gm. daily. Immediately prior to an attack the output is usually lessened. During the height of an attack the amount of uric acid excreted is increased. When food rich in purins is taken, the percentage of purin excreted is usually much less than normal, but as this low output may occur in other conditions it is not conclusive evidence of gout.

Treatment.—Prophylactic.—A patient with a family history of gout or one who has had an attack earlier in life should be abstemious in eating and drinking. He should avoid becoming heavier than is normal for his age and height. Active exercise in the open air should be taken regularly.

Dietetic.—After the diagnosis of gout has been definitely made the patient should be placed on a purin-poor diet. This means practically a lacto-vegetable diet. Meat and fish should be avoided. The meats which contain most purin are sweetbreads, liver, and kidney. While the diet should be poor in purins, care should be taken that it is not poor in protein as well. In patients with normal kidneys the effect of a high protein diet may be tried, as Folin and his co-workers have shown that this lowers the uric acid content of the blood and increases the output in the urine, probably by stimulating the kidney to excrete more uric acid. All fruits should be eaten freely. The quantity of food should be restricted. In gout the quantity of food is almost as important as the quality. The patient should be instructed to drink plenty of water, a quart or more daily. The diuretic effect of water does not increase the output of uric acid as is commonly thought. Mineral waters are often highly extolled, but they are not known to have any value in gout except that of plain water. Much of the humbuggery of the profession, as Osler says, still lingers about the use of mineral waters in gout.

Drug.—Cinchophen (atophan) is the best remedy for gout. It relieves the pain quickly. The usual dose is 3 gm. a day. It is well to take this in divided doses—0.5 gm. every two hours. Cinchophen increases the output of uric acid when first administered. This increase continues usually for only a day or two, but in some cases for ten days or more. It is advisable to determine the uric acid output daily after giving cinchophen, and to continue administration of the drug as long as the excretion of uric acid is above the previous level. The increased output of uric acid is succeeded by a fall, which is often as great as the previous rise if the administration of the drug is not stopped. In chronic gout, cinchophen should be given one or two days a week. If cinchophen causes indigestion neocinchophen (tolysin) should be given in its place, as this drug does not disturb the stomach. The usual dose is 0.5 gm. four to six times a day. Sodium salicylate and aspirin are sometimes useful in relieving the pain. A lacto-

vegetable diet contains an excess of alkali and it is well to overcome this by giving dilute hydrochloric acid—1 or 2 c.c. three times a day.

Treatment of an Acute Attack.—Usually nothing is gained by covering the affected joint, but if it is extraordinarily tender it may be protected from jars by cotton wool. To relieve the intense pain a large dose of opium or one of its derivatives should be given at once. This may be followed by either colchicum or cinchophen. It is perhaps wise to give the preference to colchicum for the first forty-eight hours. Then cinchophen may be employed in the usual dosage. The wine of colchicum or the alkaloid colchicin is usually employed. The dose of the latter is 1 mgm. Two or three pills should be given the first day and the same number the second day. When the pain is relieved or the bowels become loose this medication should be discontinued. The diet during an acute paroxysm of gout should be restricted to milk, toast, cereals, rice, lemonade, and orangeade.

Surgical Treatment.—Discharging painful tophi should be excised. The wound heals well if the incision is made through healthy tissue and the deposits of urates completely removed.

Joseph H. Pratt.

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DIABETES MELLITUS

Definition.—Diabetes mellitus is a metabolic disease characterized by deficient production of insulin by the pancreas. Since normal oxidation of carbohydrate is impossible without this substance, such loss of pancreatic function causes an increase in the concentration of sugar in the blood (hyperglycemia), with consequent secretion of excess of sugar in the urine (glycosuria). With this disorder of carbohydrate metabolism disturbances of protein and fat metabolism are frequently associated.

Etiology.—The cause of the disease is unknown, although several factors generally associated with its onset in all probability exert a definitely predisposing influence.

Obesity.—The most important of these is obesity. Joslin has pointed out that the incidence of *diabetes mellitus* is higher in individuals who are heavier than normal for their height and age. His analysis of 1000 cases of diabetes shows that "the maximum weights of only 10 per cent. of these patients were below the standard weight zone, while 15 per cent. came in

that zone and 75 per cent. above it." One hundred and twenty-four diabetics out of 196 below the age of thirty (63 per cent.) were either of normal weight or below. It may, therefore, be concluded that among children and young adults diabetes is more common in individuals of normal or subnormal weight. Among the diabetics over thirty years of age, on the other hand, the weight of only 17 per cent. was normal or subnormal at the onset of the disease, while the weight of 83 per cent. was above normal. Obesity is almost always due to overeating, and in diabetic patients the type of overeating is usually excessive indulgence in carbohydrate. Joslin's statistics (Table I) show that the consumption of sugar in this country is rapidly increasing. The fact that the percentage increase in the diabetic death rate is not correspondingly great may be explained by earlier recognition and better treatment of the disease.

Table I

THE CONSUMPTION OF SUGAR IN THE UNITED STATES

Years.	Pounds per capita. Yearly average.	Diabetic death rate per 100,000. First and last years of decades.	
1850–1860	26		
1860–1870	23		
1870–1880	33		
1880–1890	44	2.8	5.5
1890–1900	56	5.5	9.3
1900–1910	65	9.7	14.9
1910–1920	82	14.9	16.1
1921	84	16.8	

Race.—Another factor which has seemed to influence the incidence of diabetes is race. Most observers agree that Jews are more susceptible to the disease than other peoples, but it is improbable that this particular susceptibility is anything more than evidence of the fact that they prefer a carbohydrate diet and lead sedentary lives. Diabetes is thought to be rare in countries where the carbohydrate consumption is low. It is comparatively uncommon in negroes.

Sex.—Men are, on the whole, more subject to the disease than women, but among the writer's patients over forty years of age females preponderate in the proportion of 3 to 2.

Exercise.—Since lack of physical activity is an important factor in the production of obesity, it is also a factor in the etiology of diabetes.

Infections.—Some authors ascribe considerable importance to the part played by acute infections in the production of diabetes, and it is well known that a diabetic's tolerance for carbohydrate is temporarily and sometimes permanently lowered by an infectious disease. Peters particularly has emphasized the frequency with which diabetes develops after an acute infection. Joslin, however, has found an association between diabetes and acute infectious diseases in only 15 per cent. of 400 cases; and the writer has seen only 8 cases of diabetes which originated within five weeks after the onset of an infection. All of the latter group of patients are known to have been sugar-free before the infection occurred.

Syphilis, tuberculosis, gout, and diseases of the liver are all associated with diabetes, but there is no evidence that they play an important part in its etiology. Hyperthyroidism and disturbances of pituitary function also accompany the disease at times, and some authors have ascribed to them a causative rôle. While it is true that such disturbances precede the

onset of diabetic symptoms in a few cases, there is no justification for believing that they are important etiologically.

Heredity.—Statistics compiled by various authors show that the parents of patients with diabetes have themselves had diabetes in between 8 and 25 per cent. of cases. Such figures are, however, subject to considerable criticism. Ignorance of the patient about the occurrence of the disease in his ancestors and the absence of reliable statistics demonstrating the incidence of diabetes in the parents of non-diabetic individuals preclude the possibility of drawing definite conclusions. Most observers are agreed that when diabetes develops in the offspring of a diabetic it is apt to be more mild than that which develops in the offspring of a non-diabetic individual.

Nervous influences include all disturbances of emotion, such as fear, anger, and worry, as well as mental fatigue, and mechanical trauma of the nervous system. The part which they play in the production of diabetes has always been thought important, a theory to which Claude Bernard's famous piqûre experiment has lent suggestive confirmation. He showed in experiments on animals that piqûre (trauma to the floor of the fourth ventricle of the brain) evokes glycosuria, provided the glycogen stores of the body are full. It is well known that injuries to the brain or extreme emotional disturbances produce in human beings a type of glycosuria which is usually transitory. There is, however, very meager evidence that injuries of the nervous system produce true *diabetes mellitus*. Simultaneously with the onset of acute diabetic symptoms trauma to the nervous system has occurred in some cases, but even in such instances it is impossible to say that the background of the disease did not previously exist. As a matter of fact, glycosuria has existed prior to injury of the nervous system in many instances. A case cited by Foster is interesting as an illustration of the possible action of trauma to the nervous system in producing diabetes:

> A boy four years old was in a runaway accident a month before observation. He was uninjured, but badly frightened, and on the day following the accident began to drink large quantities of water. As the thirst and excessive urination continued, a physician was consulted. Sugar was found in the urine. The child lived but four months after the fright.

Morbid Anatomy.—Diabetes is caused by a functional disturbance of the islands of Langerhans in the *pancreas*. The so-called β-cells of the islands normally contain granules, but Bensley has found these to be lacking in most cases of diabetes. The space which they should occupy becomes filled with fluid. This gives the cells a vacuolated appearance and is known as *hydropic degeneration*. The process may continue until the islands are completely destroyed. Fibrosis and hyaline degeneration of the islands of Langerhans are also common pancreatic changes in diabetes and are probably sequelæ of the death of the cell following hydropic degeneration. One or another of these types of degeneration eventually reduces the total number of islands in the pancreatic tissue.

The definite lesions in the islands of Langerhans in diabetes are, therefore, hyalinization, fibrosis, or hydropic degeneration of the β-cells. When the latter change exists, it can be shown only when the pancreatic tissues are appropriately stained within a few hours after death. The failure to obtain autopsies in this period probably explains why in so many instances the islands appear histologically normal at autopsy even in cases of severe

diabetes, rapid autolysis of tissue after death being especially striking in the pancreas. An excellent summary of the morbid changes in the pancreas has been made by Cecil. He has classified the lesions found in 90 cases as follows:

	Cases.
Chronic inflammation of the pancreas:	
Interacinar pancreatitis; sclerosis of islands of Langerhans	39
Interlobular pancreatitis; sclerosis of islands of Langerhans	4
Interacinar pancreatitis; hyaline degeneration of islands of Langerhans	19
Interacinar pancreatitis with lipomatosis; sclerosis of islands of Langerhans	2
Interacinar pancreatitis with lipomatosis; hyaline degeneration of islands of Langerhans	1
Interacinar pancreatitis with hemochromatosis	2
Parenchyma normal:	
Sclerosis of islands of Langerhans	4
Hyaline degeneration of islands	7
Infiltration of leukocytes about islands	1
Pancreas normal	11

In the total number of cases studied, only 11 (12 per cent.) showed no change in the islands of Langerhans. As Cecil was unable to avail himself of the more delicate staining methods subsequently used for depicting changes in the β-cells, it may be that there were lesions in the islands in even a greater number of patients.

The *liver* is sometimes enlarged and may show fatty degeneration.

Physiology.—It remained for Banting and his co-worker Best to demonstrate beyond doubt that a hormone necessary for the oxidation of glucose was produced by the pancreas. This hormone has been named insulin. That total pancreatectomy in animals produced fatal glycosuria analogous in many respects to that found in man was demonstrated by Minkowski forty years ago, but in spite of this and repeated efforts to make insulin from pancreatic tissue, all attempts had yielded negative results. Failure to recover insulin from the pancreas was in most instances due to technical difficulties in removing proteolytic enzymes. Banting availed himself of the well-known fact that ligation of the pancreatic ducts in dogs is followed in from six to eight weeks by complete destruction of the acinar tissue in the pancreas, while the islands of Langerhans remain intact. Thus the production of trypsin, the proteolytic enzyme formed by the acinar cells of the pancreas, is completely eliminated. From the pancreatic tissue thus treated Banting was able to isolate insulin in a relatively pure form, which, when injected into diabetic animals and man, lowered blood-sugar and reduced or abolished glycosuria.

Insulin for clinical use is prepared from the pancreas of large animals, such as sheep, hogs, and cattle, the fresh tissue being immediately treated with certain concentrations of acidified alcohol or acetone which nullify the proteolytic action upon insulin.

The value of insulin in glucose oxidation is measured by the "unit." This "unit" is the amount of insulin which, when administered subcutaneously after a twenty-four-hour fast to rabbits weighing 2 kilograms, produces convulsions within four hours. This is the so-called "physiological unit." The clinical unit is one-third of this amount.

Insulin is secreted by the normal pancreas at a fairly uniform rate. The flow increases after meals, particularly after ingestion of carbohydrate food. The exact mode of action of insulin on the glucose in the blood-stream and in the tissues is not fully understood, although it is known that

this hormone oxidizes sugar and is also able to convert a monosaccharid (sugar) into a polysaccharid (glycogen).

In the metabolism of sugar and starches in the intestinal tract the polysaccharids, disaccharids, and some of the monosaccharids of the food are converted into glucose, absorbed through the wall of the intestine, and carried in the portal blood to the liver. Most of the sugar, perhaps all, is reconverted by the hepatic cells into the polysaccharid, glycogen, and stored. The unchanged glucose with the larger part of the glucose reconverted in the liver is then carried, as such, to the muscles, where it is stored as glycogen. When needed to produce heat and energy these glycogen stores are converted by successive stages into glucose, transported by the blood-stream to the various tissues of the body, and finally broken down to water and CO_2. The formation of lactic acid is one of the intermediate stages of this destruction of the glucose molecule. During this process of oxidation, heat is produced.

When the supply of insulin is deficient, part of the sugar available for the organism cannot be properly oxidized or reconverted into glycogen, and consequently an excess of glucose accumulates in the blood-stream. The degree of hyperglycemia depends on the degree of the insulin deficiency, and the amount of available glucose, and these two factors in turn determine the amount of excess sugar in the urine. When oxidation of glucose completely ceases, all the carbohydrate in the food is excreted as glucose, together with glucose formed from protein and whatever moiety may be derived from fat.

The total quantity of glucose available for the body is derived from both the body tissues and the food. In conditions of undernutrition or starvation, or whenever "exogenous" food fails to maintain the body requirements, "endogenous" food, that is, the carbohydrate, protein, and fat of the tissues, is used to provide energy. Fifty-eight per cent. of the protein and, according to Woodyatt, 10 per cent. of the fat can be converted into glucose, whether they are "endogenous" or "exogenous." The total potential glucose supply in normal and diabetic individuals is, therefore, 100 per cent. of the endogenous and exogenous carbohydrate plus 58 per cent. of the protein and 10 per cent. of the fat derived from both these sources. Since 1 gm. of nitrogen is excreted in the urine for each 6.25 gm. of protein (animal or vegetable) destroyed, and since 3.65 gm. of glucose is derived from each 6.25 gm. of protein, it is possible to determine whether or not the ability to oxidize sugar is completely lost. If a diabetic patient excretes in the urine 3.65 gm. of glucose for every gram of nitrogen during a period of five days or more while the diet consists merely of protein and fat, or during starvation, there is reasonable certainty that, temporarily at least, no sugar from whatever source can be utilized by the tissues.

Nitrogen Balance.—When, during a given interval, the nitrogen intake equals the nitrogen loss, the patient is said to be in nitrogenous equilibrium. When the nitrogen intake exceeds the output there is a "positive nitrogen balance"; and when the condition is reversed, a "negative nitrogen balance." Protein is the only available source of nitrogen.

There is no great unanimity of opinion regarding the *protein requirements* of normal individuals. The average healthy adult instinctively eats between 1 and 1.5 gm. of protein per kilo of body weight, and the usual estimate of the protein needs of a diabetic adult has consequently

come to be 1 gm. of protein per kilo unless there is some complicating disease which necessitates reduction of the protein consumption. The author has usually considered the protein requirement of diabetics to be approximately 1.25 gm. per kilo of body weight. In older patients who lead inactive lives, 1.0 gm. per kilo of body weight or less is sufficient; in growing children between 2 and 3 gm. per kilo is commonly accepted as the standard. The quantity of protein actually used by an individual can be accurately determined by comparing the nitrogen content of the food with the sum of the output of nitrogen in the urine and feces.

The Caloric Requirement.—In diabetics the caloric requirement is, as a rule, somewhat lower than normal. This is fortunate, for the quantity of carbohydrate which can be taken is often so reduced that even protein and fat cannot be given in amounts large enough to compensate for the loss. In severe diabetes the carbohydrate intake must often be reduced to 20 gm. a day if the urine is to be kept free from sugar. When the condition is mild, however, 100 gm. or more are often tolerated. Very few diabetics can take more than 200 or 250 gm. daily except for very short periods, and the majority are restricted to a daily intake of between 70 and 120 gm. The *average normal diet* in this country consists of 400 gm. of carbohydrate, 100 gm. of protein, and 100 gm. of fat, and yields approximately 2900 calories, 55 per cent. of which are derived from carbohydrate. It is obvious that if in diabetes the carbohydrate tolerance is below 100 gm. the caloric intake is much reduced unless extra protein and fat can be taken to provide the calories usually derived from carbohydrate. Such an increase in the protein consumption is possible, but, except to a limited extent, inadvisable for the following reasons:

1. Protein itself yields glucose in its catabolism (58 per cent.), and a large increase in protein would yield too much glucose.

2. The high specific dynamic action of protein would necessitate an increase in the total caloric intake quite out of proportion to the number of calories provided by the additional protein.

3. Each gram of protein yields more glucose and half as many calories as does each gram of fat when it is burned in the body; therefore the quantity of protein calories necessary to compensate wholly for carbohydrate calories lost would be correspondingly greater than that of fat, and would be so great as to make the diet unpalatable.

4. Ingestion of such large quantities of protein for long periods is probably injurious to the kidneys and arteries.

The fat consumption is limited only by the gastro-intestinal tolerance and by the keto-antiketogenic ratio, which must be such as to prevent ketonuria. Fat is, therefore, the food substitute of choice to provide calories when carbohydrate tolerance is low. Prior to the use of insulin in diabetic therapy it was essential to raise the fat intake to between 100 and 300 gm. in order to furnish adequate calories. With insulin the greatly increased quantity of carbohydrate food that may be fed renders the substitution of fat calories for carbohydrate calories proportionately less necessary.

The Effect of the Protein and Fat Intake on the Carbohydrate Tolerance.—In diabetes the carbohydrate tolerance is usually affected by the intake of protein and fat. The total quantity of glucose in the diet is estimated as the total of the carbohydrate plus 58 per cent. of the protein and 10 per

cent. of the fat. Thus, 50 gm. of carbohydrate, 70 gm. of protein, and 200 gm. of fat contain approximately 110 gm. of glucose; and 50 gm. of carbohydrate, 50 gm. of protein, and 100 gm. of fat supply about 88 gm. of glucose. Ingestion of large quantities of fat for long periods reduces the tolerance for glucose in experimental animals and in diabetic patients. This effect of fat upon diabetic tolerance may not be due to fat *per se* nor to the glucose formed from it, but rather to the increased calories or "food units" fed, with resultant increase in body weight. It is impossible to define definitely the limits of a "large quantity of fat" because while 100 gm. or more may be a large amount for a child or small adult, 200 gm. is not a great deal for a large, vigorous adult. Roughly speaking, however, in an adult a fat intake above 150 gm. may be considered large.

In the adjustment of a diabetic diet another effect of the ingestion of fat must be considered in order to avoid *ketosis and subsequent acidosis*. For the oxidation of one molecule of fatty acid, one molecule of glucose or less is necessary. If less than this amount of glucose is utilized or if the diet contains additional fat, ketone bodies appear in the blood and urine. When this occurs, the development of true acidosis depends on the quantity of excess ketone substance, the ability of the kidneys to remove the excess, and the ability of the blood to transport to the lungs the carbon dioxid which has been formed and displaced from basic radicals. This displacement is the result of the substitution of the stronger ketone acids for the weaker carbonic acid. The carbon dioxid thus freed is eliminated by the lungs. When the blood can no longer transport all the excess CO_2 to the lungs, "acidosis" results. Such an acidosis is characterized by the presence of ketone bodies in the blood-stream. As these are brought to the kidney they are dissociated from the basic radicals and excreted as ketone acids or salts of ammonia. Thus it is seen that although the presence of an excess (above normal) of ketone bodies in the blood (hyperketonemia or ketosis) is usually associated with a lowering of the CO_2 combining power of the blood, or "acidosis," a certain degree of hyperketonemia with ketonuria may be present without any alteration in the reaction of the blood. This is termed ketosis without acidosis.

Ketogenic-antiketogenic (Ketolytic) Ratio.—From the foregoing it will be seen that in order to prevent ketosis a certain minimal oxidation of glucose is necessary for the proper combustion of a given amount of fat, and that all food mixtures (whether of endogenous or exogenous origin) yield definite amounts of ketogenic and ketolytic materials. Several formulæ have been devised which express the percentage of ketolytic and ketogenic substance which can be derived from a given amount of each great group of food substances, carbohydrate, protein, and fat. These formulæ also are roughly indicative of the quantitative relationship that must exist between the two in order to produce or prevent ketone production. For example, the formula of Woodyatt,

$$\frac{\text{100 per cent. carbohydrate + 58 per cent. protein + 10 per cent. fat}}{\text{90 per cent. fat + 46 per cent. protein}}$$

in which the numerator represents *ketolytic substance* and the denominator *ketogenic substance*, should when applied to the planning of diets yield a relationship of 1 gm. of ketolytic substance to not more than 1.5 to 1.8 gm. of ketogenic substance in order to prevent ketosis. Relationships of over

1 to 1.8 produce ketosis, whereas ketosis is never encountered when the ratio is below 1 to 1.5. Woodyatt claims that ratios above 1 gm. glucose to 1.5 gm. fat usually produce ketonuria in diabetes. Therefore, from the equation above, the maximum amount of fat to be fed is represented by the equation $F = 2C + P/2$. Practically, however, considerably larger amounts of fat in relation to glucose may be fed without causing ketonuria; and as a matter of fact, in most cases, if the amount of protein is kept at 1 gm. per kilo of body weight the amount of fat allowed may be three to four times the amount of carbohydrate without producing ketonuria. The formula of Palmer and Ladd is much simpler, *i. e.*, G = 100 per cent. C + 58 per cent. protein and F = 100 per cent. F. With this formula F may be from three to four times G before ketonuria develops.

Ketonuria and Ketonemia.—Normally the quantity of acetone bodies in the blood varies greatly (3 to 200 mgm. per 100 c.c. of blood). When the concentration of ketone bodies in the blood is within normal limits, these substances are not excreted in the urine, at least as far as can be detected by delicate qualitative methods (Rothera test). True hyperketonemia exists when the acetone content of the blood is above 200 mgm.

The presence of ketone acids in the urine may be detected qualitatively by the nitro-prussid or ferric-chlorid tests. In mild acidosis the quantity of ketone acids excreted in the urine in twenty-four hours may vary from 0.5 to 5.0 gm.; and in the more severe forms it may amount to 30 or even 40 gm. per day, although an excretion of ketone substances not over 5 or 6 gm. per day is sometimes observed in severe diabetic acidosis.

The Excretion of Ammonia in the Urine.—In most conditions associated with acidosis, and particularly in diabetes, the body is able to form an additional base (organic) unlike most of that normally present in the body (inorganic base). This additional organic base (ammonia) is formed by the kidneys to neutralize the excess acid and thereby aid its elimination. It appears in large amounts in the urine of diabetics with severe acidosis. The average normal excretion is 0.65 gm. per day; during diabetic acidosis, ten times this amount of ammonia or even more, according to the severity of the acidosis, is excreted in the urine.

Blood Sugar.—The sugar content of the normal whole blood during fasting ranges from 80 to 120 mgm. per 100 c.c. In diabetes it may be normal or high (120 to 800 mgm. per 100 c.c.). The blood sugar normally rises after meals, and is usually highest between fifteen minutes and an hour after eating. The maximal postprandial content is rarely more than 140 mgm. per 100 c.c.; if, however, it is 160–180 mgm. sugar may appear in the urine. This is the so-called *renal threshold* for sugar and varies in different individuals. The rise in blood-sugar content after the noon and evening meals is usually less than that which follows the morning meal. The duration of the elevation is more significant than the degree. It is usually somewhat less than two hours. If the content of blood sugar has not returned to normal after this interval, the patient may be diabetic even though the immediate rise is within normal limits. If both the degree and the duration of the hyperglycemia are beyond the normal postprandial limits, there should be strong suspicion of diabetes, although subjective symptoms of the disease are absent and there is no sugar in the urine. The blood-sugar curve of diabetic children, particularly in the early stages of the disease, may fall within the limits normal for adults. The postprandial

content is not infrequently between 120 and 140 mgm. per 100 c.c., and yet sugar is present in the urine. In certain long-standing cases of diabetes and in the severe acute stages of the disease, the blood-sugar content may be very high (350 mgm. per 100 c.c.) during fasting or after meals, and yet the urine remain sugar-free. This condition is spoken of as an increased renal threshold for sugar.

Under adequate treatment without insulin, the fasting blood sugar of diabetic patients (in the morning) is usually within normal limits (80 to 120 mgm. per 100 c.c. of blood); and if glycosuria is avoided, the quantity of sugar in the blood three or four hours after meals is sometimes normal, although the drop in blood sugar may be characteristically delayed. In severe or long-standing diabetes the blood-sugar content is often high throughout the day in spite of the absence of sugar in the urine. It should be emphasized that the degree of glycemia in normal and diabetic individuals is not stationary, but varies greatly during twenty-fours, particularly in diabetics. Consequently, in any interpretation of the content of sugar, the time of the previous meal and its carbohydrate content, as well as the diet of the preceding day, must be considered.

Blood Fat.—Under the heading "blood fat" are included all the lipoid substances normally present in blood. These are: first, glycerids of the fatty acids, such as oleic, palmitic, or stearic; second, lecithin; and third, cholesterol with its esters. The average normal total lipoid content of the blood is 0.68 grams per 100 c.c., variations being from 0.57 to 0.76. These variations after high fat feeding in normal people are often more extreme. In diabetes the blood fat may rise to 13.1 grams per 100 c.c. of blood. A marked increase in blood fat may appear without producing a milkiness of the serum, but in most instances this milkiness or lipemia usually appears when the lipoid content is as high as 0.8 per cent. When there is hyperlipemia most of the lipoid increase is found in the plasma. The postprandial increase after high fat feeding is usually delayed for from three to six hours. As a rule, significant increases in blood fat are observed only in severe forms of diabetes, particularly during acute acidosis. Nothing definite is known as to the cause of the increase of lipoids in the blood during diabetes, but in view of the fact that any increase can be reduced to normal by proper therapy it is assumed that the change is in some way secondary to the disturbances in carbohydrate metabolism.

The Respiratory Quotient (R. Q.).—Just as the volume of oxygen consumed during a given period of time is an index of the total heat production in the body, so may the relation of the volume of carbon dioxid exhaled to the volume of oxygen inhaled be a measure of the quality or nature of the metabolic changes which are taking place. This relationship of CO_2 excretion to oxygen consumption is known as the "respiratory quotient" (the Co_2 is the numerator and the O_2 the denominator). When food is burned in the body a certain amount of oxygen is required and a certain amount of carbon dioxid is produced. The quantitative relationship between these two substances is always a constant for each one of the three foods—carbohydrate, protein, and fat—or for any other combustible substance. For example, carbohydrate ($C_6H_{12}O_6$), in order to have enough oxygen to form its end-products CO_2 and H_2O, requires for its combustion within the body $6O_2$; in other words, the structure of the carbohydrate molecule is such that oxygen is required for the carbon alone; in the case of fat,

O_2 is required for carbon and also for a large quantity of hydrogen, so that the denominator is increased, the quotient being 0.71; protein occupies an intermediary position, *i. e.*, gives a quotient of 0.81. Alcohol (C_2H_6O) has a respiratory quotient of 0.67; β-oxybutyric acid ($C_4H_8O_3$) of 0.89; diacetic acid ($C_4H_6O_3$) of 1.00; and acetone (C_3H_6O) of 0.75.

The average respiratory quotient in normal individuals after a fourteen- to sixteen-hour fast is usually between 0.81 and 0.83. In diabetes, depending upon the severity, quotients may vary under similar conditions between 0.68 and 0.81, the lower quotients representing a total inability to oxidize glucose from any source.

Symptoms and Signs.—The onset of diabetes is usually so gradual that the disease may be unnoticed for months or even years, although the symptoms and signs are quite characteristic. Six of the most typical manifestations are polyuria, polydipsia, polyphagia, loss of weight, weakness, and pruritus. Glycosuria and hyperglycemia are the fundamental abnormalities to which most of the subjective symptoms are referable and, when they are accompanied by the objective symptoms just mentioned, are pathognomonic of the disease.

Polyuria is often the first symptom noticed by the patient. Ten liters of urine or even more may be passed in twenty-four hours, although the usual quantity is between 3 and 6 liters. In many early, mild conditions, however, the urinary output is not increased. The polyuria may be explained in large part by the diuretic effect of sugar. The fluid intake usually corresponds closely to the urinary output.

Polydipsia.—The polydipsia, which is a very common symptom, results from the presence in the blood of large quantities of sugar which in turn withdraws fluids from the tissues and thereby establishes the consequent need for its replacement.

Polyphagia.—The appetite is often enormous, and roughly proportional to the quantity of sugar lost in the urine. When the disease is mild, however, and particularly when the patient is elderly, there is apt to be no increase in the appetite, but, in some cases, an actual decrease.

Loss of Weight.—The loss of weight may be very slight or amount to 80 pounds in two or three months. Usually between 10 and 20 pounds are lost within two months.

Weakness.—The degree of weakness is often roughly proportional to the loss of weight. Both of these symptoms are originally due to the loss of food which results from inability to oxidize sugar.

Pruritus may be general, but in women is usually confined to the genitalia.

Laboratory Observations.—*The Urine.*—The specific gravity of the urine is usually increased to between 1.025 and 1.045. The color is very pale, the odor sweetish, and the glucose content variable. If the diabetes is mild, tests may demonstrate the presence of only a trace, or less than 2 per cent. of sugar, but when it is severe, the content may rise to 10 per cent. As much as 500 or 600 gm. may be excreted in twenty-four hours. Albumin is sometimes present, but is not due to the diabetes except in acidosis. The presence or absence of "ketone bodies" (acetone, diacetic acid, and β-oxybutyric acid) depends largely on the severity of the disease, the character of the diet, infections, and other factors. The presence of these substances is evidence of ketosis.

The Blood.—The erythrocyte count may be somewhat higher than normal, but the leukocyte count remains unchanged unless intercurrent infection sets in.

Types of Diabetes.—Diabetes may be divided for convenience into two types, the mild and the severe. The *mild type* is not inherently fatal unless complicated by acidosis. The tolerance for food permits the patient to live on a diet which contains enough calories to supply the bodily needs. Any patient who can take 50 to 80 gm. of carbohydrate with protein and fat to provide a maintenance diet, remains sugar free, and maintains weight and strength for between one and five years, usually has a mild type of diabetes. This is most commonly seen in middle-aged and elderly individuals, is rare in young adults, and almost unknown in children. The *severe type* is characterized by an acute onset and rapid downward course with fatal outcome in spite of all dietary restrictions. It occurs most often in children and young adults, and is rare in individuals more than forty years of age. This type is more frequently complicated by acidosis than is mild diabetes. The glycosuria is usually controlled with great difficulty.

Complications.—Chronic Acidosis.—The most common and dreaded complication of diabetes is acidosis. It may be classified as mild or chronic, and severe or acute. In the chronic type, which is the less severe, the CO_2 content of the blood sometimes falls from 50 volumes per cent. to as low as 40 volumes per cent., accompanied by glycosuria and ketonuria. This may persist for weeks or even months without change, and produce characteristic symptoms which are usually not alarming. The most outstanding are easy fatiguability, lack of appetite, inconstant headache, and general languor and lack of ambition. *Diabetic neuritis*, which is usually associated with this form of acidosis, is characterized by shooting pains or a dull ache along the distribution of the peripheral nerves, especially in the lower extremities. This pain becomes worse at night; the superficial reflexes are often diminished or absent and sensory paresthesias are common. These latter changes have given rise to the term "diabetic tabes." This so-called *diabetic neuritis* usually disappears very soon after the urine becomes free from sugar and ketone acids.

Acute Acidosis.—At the onset of acute acidosis the face is often flushed, but as the condition progresses marked pallor ensues. Decrease of the intra-ocular tension produces the so-called *soft-eyeball* which is frequently associated with this type of acidosis. In addition to the symptoms evoked by the mild condition, the severe form produces nausea, vomiting, epigastric pain and discomfort, hyperpnea (Kussmaul breathing), subnormal temperature, and drowsiness finally followed by *coma*. Other evidences of severe acidosis are dryness of the skin, shrinking of the superficial tissues, and a red, glistening, beefy condition of the tongue, throat, mouth, and lips. These and other of the signs of acute acidosis can be accounted for by the loss of body fluid (dehydration). The breath has an "acetone" or "fruity" odor, the temperature is slightly above normal, the white blood count rises, often to 25,000, though the differential count may be normal, and albuminuria and cylindruria frequently develop. The CO_2 content of the blood is often extremely low; in complete coma it is known to have fallen to 6 volumes per cent. The appearance of extreme emaciation and the sunken features are further evidence of the marked drying of the tissues. This desiccation increases the concentration of acid in the body tissues.

Cardiac failure with marked lowering of the blood-pressure (in some cases to 60–50 mm. Hg during systole) is common when the acidosis is fatal. This is very often accompanied by complete anuria, and in rare instances is followed by convulsions.

Furunculosis and Carbunculosis.—Furunculosis was a very common complication of diabetes before modern methods of keeping the urine free from sugar were employed. The incidence of carbunculosis, which tends to involve the posterior cervical and upper dorsal regions, has similarly decreased.

Tuberculosis.—Diabetic patients are somewhat more susceptible to pulmonary tuberculosis than are normal people—a fact which is probably related to the state of undernutrition and has no other significance. Fortunately, insulin makes it possible to treat tuberculosis with diabetes just as it is treated alone and has, therefore, rendered the prognosis more favorable.

Other Conditions Associated with Diabetes.—Certain conditions such as retinitis, cataract of the eye, and ulcers and gangrene of the extremities, particularly of the feet, also frequently accompany diabetes. It is generally believed today that these are not entirely dependent on the diabetic state for their existence. *Perforating ulcer* and *gangrene (wet or dry) of the foot*, for example, are often associated with very mild diabetes and may be in no wise affected by control of the glycosuria. Usually marked arterial changes can be shown to be responsible for the gangrene. *Arteriosclerosis* develops to some extent in almost every middle-aged or elderly diabetic patient, and many observers believe that the long-continued hyperglycemia plays a certain etiological rôle in the condition. Its common occurrence in elderly non-diabetic individuals, however, renders the causative effect of diabetes improbable.

Diagnosis.—Diabetes mellitus can usually be diagnosed by the demonstration of sugar in the urine. Benedict and Osterburg, as well as Folin and Berglund, have demonstrated, however, that a reducing substance is present in the urine of all normal individuals. Part of this is fermentable and is presumably glucose. Its chemical identification involves a more delicate test than that with ordinary Benedict's qualitative solution. Benedict has termed this condition "*glycuresis*." Glycuresic urine contains from 0.5 to approximately 2 gm. of glucose in twenty-four hours. Differentiation of diabetes mellitus from renal glycosuria, alimentary glycosuria, lactosuria, and other glycosuric states depends for the most part on blood-sugar tests and qualitative and quantitative examination of the urine designed to distinguish the identity of the reducing substances.

The term *renal glycosuria* has been applied to a relatively rare condition which may be distinguished from diabetes by the constancy of the glycosuria regardless of the carbohydrate intake, the normal quality of the variation of the blood sugar, and the absence of other symptoms of diabetes. Observation of patients with this condition over prolonged periods shows that a certain number develop true diabetes mellitus, while others apparently continue to have unquestioned renal glycosuria for years. *Alimentary glycosuria* includes conditions in which there is a trace of sugar in the urine after excessive carbohydrate ingestion, undue emotional stress, or a combination of the two. The maximal and immediate blood-sugar content in individuals subject to this disturbance is usually supernormal,

after the ingestion of glucose, but the return to normal usually occurs about two hours after meals. This condition may persist for many years without leading to diabetes mellitus. The ability to oxidize carbohydrate, as determined by the respiratory quotient, remains normal, a fact which is important in differentiating renal and alimentary glycosuria from diabetes.

Pentosuria, a rare condition which is usually familial, may be recognized by the identification of pentose in the urine. Galactosuria, maltosuria, and levulosuria are also rare conditions while lactosuria is usually observed only in lactating women. The blood-sugar content is not increased in any of these latter conditions. They are all without pathological significance.

Prognosis.—There is no good evidence that diabetes is ever cured. A certain number of young patients and a very few older diabetics are said to have been cured, but such reports are very rare, and probably signify only that the disease has been arrested. The variations in carbohydrate tolerance to which a patient is always subject may be so marked that a mere remission is mistaken for complete recovery. The following example of this may be of interest:

> A woman fifty-two years of age who had suffered from mild diabetes for ten years had an attack of influenza. Glycosuria and ketonuria developed and persisted, even when the diet was restricted, for six months. At the end of this time the urine was made sugar-free by starvation, and a tolerance of 35 gm. of carbohydrate with approximately 1600 calories was established. This could not be raised for many months, but finally after another six months it was possible to increase the carbohydrate intake gradually to 450 gm. with 2400 calories without producing glycosuria or hyperglycemia. This tolerance persisted for six weeks and at the end of that time there were only faint traces of sugar in the urine. A year and a half later the patient was able to take 150 gm. of carbohydrate and no more, and at this point her tolerance has remained.

The discovery of insulin has undoubtedly done much to brighten the prognosis in diabetes. A great deal still depends, however, on the full co-operation of the patient in regulating the diet and on the exercise of self-control in dietary habits.

Treatment.—A cardinal principle in the treatment of diabetes is to *keep the urine free from sugar*. This has been attempted from the very beginning of diabetic therapy, but in a certain number of patients the severity and persistence of the glycosuria has been such that it was not always possible without what was considered dangerous or impracticable dietary restriction. In 1914, however, Allen advocated the use of a degree of undernutrition that had before been considered dangerous. He showed that more or less complete deprivation of food is necessary to overcome glycosuria and acidosis in certain severe cases; and that once this has been accomplished, the food intake can be somewhat increased although it is still essential to restrict the number of calories so that marked undernutrition continues. This was a very important advance in therapeutic methods, but did not so completely revolutionize the treatment as did *Banting's discovery of insulin* in 1922. Injection of this substance permits the patient to live on a maintenance diet even when the diabetes is very severe, and consequently allows the weight and strength to be kept almost normal. It does not, however, do away with the need of regulating the food intake.

There are certain definite factors which govern the *caloric requirements* of the body and determine the quantity of food necessary, *i. e.*, sex, age, weight, height, and body surface. The degree of activity of the individual

also calls for corresponding variations in the number of calories used. The *surface area of the body* is most satisfactorily determined by using the Du Bois chart (Fig. 11), which is based on the formula: Area (sq. cm.) = weight$^{0.425}$ × height$^{0.725}$ × 71.84. Since the basal metabolism per square

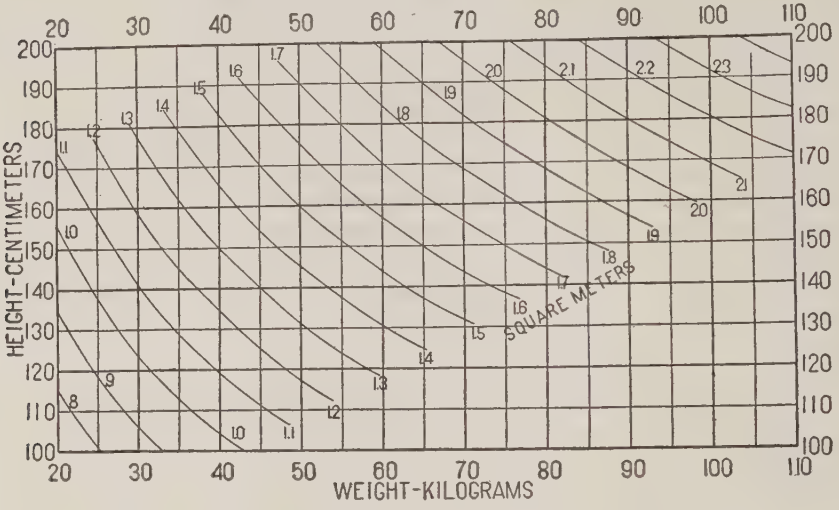

Fig. 11.—Chart for determining surface area of man in square meters from weight in kilograms (wt.) and height in centimeters (ht.) according to the formula: Area (sq. cm.) = wt.$^{0.425}$ × ht.$^{0.725}$ × 71.84. (Du Bois.)

Table II*

THE AVERAGE CALORIC REQUIREMENTS PER SQUARE METER OF BODY SURFACE IN BOTH SEXES FOR DIFFERENT PERIODS OF LIFE

Age.	Calories per square meter per hour: Male.	Female.
14–16	46	43
16–18	43	40
18–20	41	38
20–30	39.5	37
30–40	39.5	36.5
40–50	38.5	36
50–60	37.5	35
60–70	36.5	34
70–80	35.5	33

* Taken from page 122, Aub and Du Bois, Carnegie Reprint.

meter per hour varies with both the age and sex of the individual, Table II must be employed with Figure 11 to permit calculation of the minimal (basal) caloric requirements of the individual. Both the heat production and the heat requirement of the body have been found to be more nearly proportional to the surface area than to either height or weight alone. The *state of nutrition* also affects the basal metabolic rate (the number of calories expended fourteen hours or more after eating, with complete muscular and digestive relaxation). When the body is properly nourished it needs more calories than after prolonged malnutrition. Since most diabetic patients are underweight, this factor might markedly affect the calculation of the bodily needs. There is a divergence of opinion about the wisdom of keeping diabetic subjects in a state of normal nutrition or in a condition 10 to 30 per cent. below normal, but most physicians believe

that it is better for the nutrition to be between 10 and 20 per cent. below normal. The minimal requirements of the body must be augmented by between 30 and 80 per cent. to fulfil the *actual needs* of an adult individual who leads a life of average activity in the city. Children and adults engaged in heavy physical labor require an even greater increase. Perhaps the calculation of the caloric requirement can be most clearly outlined by giving an actual example:

Suppose the patient to be a man thirty-five years of age, whose weight is 70 kilograms, and whose height is 170 cm. (69 inches, or 5 feet 9 inches). In Fig. 11 it will be found that a horizontal projection of the point on the height column at 170 cm. will meet a perpendicular projection of the 70 kilogram point on the base-line at approximately 1.8 on the diagonal. This means that the surface area of the individual is 1.8 square meters. Since Table II shows that the hourly caloric requirement of a man between thirty and forty years of age is 39.5 per square meter of surface area, this patient will require 1.8 x 39.5 x 24 (hours), or 1730 calories daily under basal or minimal conditions. If the actual needs are assumed to be 50 per cent. in excess of this the daily caloric content of the food must be 2595. Such a patient might easily be 20 pounds below weight because of prolonged undernutrition. This would mean that instead of the 2595 calories needed to maintain normal nutrition, only about 2200 would be required.

After calculating the number of calories needed to maintain life, it is essential to determine whether the patient can eat sufficient food to provide the necessary heat without becoming hyperglycemic and glycosuric. Before the discovery of insulin it was thought essential to keep the urine free from sugar, even though the caloric intake was reduced far below the minimal requirement. This meant that a patient with severe diabetes gradually starved to death unless some complication like acidosis or an intercurrent disease carried him off beforehand. Now, however, the administration of insulin permits individuals with very severe diabetes to eat sufficient food to maintain almost normal weight and strength. The relative proportion of carbohydrate, fat, and protein in the diet exerts a marked effect on the tolerance of the diabetic individual. Newburgh and Marsh have demonstrated that diets which contain a relatively large quantity of fat and a small quantity of carbohydrate are better tolerated when the protein content is minimal than when it is high. Reduction of the protein intake diminishes the total glucose content of the diet and the specific dynamic action.

The dietary restrictions necessary to render the urine sugar-free vary greatly with the severity of the disease. When the diabetes is mild, only a very slight reduction of the carbohydrate intake is necessary; but when it is severe, starvation may need to continue for many consecutive days before the urine ceases to contain sugar. The sudden institution of complete fasting, particularly if the food intake has just previously been very abundant, may produce rather alarming acidosis. This occurs most often in obese individuals, or in any case when the renal function is impaired. It is, therefore, safer to proceed as follows:

First Day.—Reduce the carbohydrate intake to 100 gm., the protein intake to approximately half that of the previous régime, and the fat intake to 10 or 20 gm.

Second Day.—The carbohydrate intake may be cut in half, while the quantity of protein and fat remains unchanged.

Third Day.—Reduce the diet to approximately 30 gm. of carbohydrate, 30 gm. of protein, and 10 gm. of fat for a week or until the patient is sugar-

free. If sugar has not disappeared from the urine within five to seven days, or if rapid desugarization is desired, complete fasting may be necessary, and at this stage will not, as a rule, cause acidosis.

TABLE III

DIABETIC FOOD TABLE (Joslin)

Water, clear broths, coffee, tea, cocoa shells, and cracked cocoa can be taken without allowance for food content

FOODS ARRANGED APPROXIMATELY ACCORDING TO CONTENT OF CARBOHYDRATES

	5%		10%	15%	20%
	*Reckon average carbohydrate in 5% veg. as 3%—of 10% veg. as 6%				
VEGETABLES (fresh or canned)	1%–3%	3%–5%*	10%*	15%	20%
	Lettuce	Tomatoes	String Beans	Green Peas	Potatoes
	Cucumbers	Brussels Sprouts	Pumpkin	Artichokes	Shell Beans
	Spinach	Water Cress	Turnip	Parsnips	Baked Beans
	Asparagus	Sea Kale	Kohl-Rabi	Lima Beans	Green Corn
	Rhubarb	Okra	Squash		Boiled Rice
	Endive	Cauliflower	Beets		Boiled Macaroni
	Marrow	Egg Plant	Carrots		
	Sorrel	Cabbage	Onions		
	Sauer-kraut	Radishes	Green Peas		
	Beet Greens	Leeks			
	Dandelions	String Beans			
	Swiss Chard	Broccoli			
	Celery	Artichokes			
	Mushrooms				
FRUITS	Ripe olives (20% fat)		Strawberries	Raspberries	Plums
	Grape Fruit		Lemons	Currants	Bananas
			Cranberries	Apricots	Prunes
			Peaches	Pears	
			Pineapple	Apples	
			Blackberries	Blueberries	
			Oranges	Cherries	

1 gram protein, 4 calories.
1 " carbohydrate, 4 "
1 " fat, 9 "
6.25 grams protein contain 1 gm. nitrogen.

1 kilogram = 2.2 pounds.
30 grams (gm.) or cubic centimeters (c.c.) = 1 ounce.
A patient "at rest" requires 25 calories per kilogram.

30 Grams (1 Oz.) Contain Approximately	Carbohydrates, gm.	Protein, gm.	Fat, gm.	Calories
Vegetables 5%	1	0.5	0	6
Vegetables 10%	2	0.5	0	10
Shredded Wheat	23	3	0	104
Uneedas, two	10	1	1	53
Potato	6	1	0	28
Bread	18	3	0	84
Oatmeal, dry weight	20	5	2	118
Oysters, six	4	6	1	49
Milk	1.5	1	1	19
Meat (cooked, lean)	0	8	5	77
Fish	0	6	0	24
Chicken (cooked, lean)	0	8	3	59
Egg, one	0	6	6	78
Cheese	0	8	11	131
Bacon	0	5	15	155
Cream, 20%	1	1	6	62
Cream, 40%	1	1	12	116
Butter	0	0	25	225
Oil	0	0	30	270

As soon as the urine is completely free from sugar, the patient may receive a low calory diet, or start with 30 gm. of carbohydrate, 30 gm. of protein, and 20 gm. of fat, and increase the food consumption daily according to some such schedule as the following: Second day, carbohydrate 30, protein 50, fat 60 gm.; third day, carbohydrate 30, protein 60, fat 80 gm.; fourth day, carbohydrate 30, protein 1 gm. per kilo, and fat to make the total number of calories equal to the basal requirements plus 10 per cent. If this does not cause glycosuria, the carbohydrate intake may be raised 10 gm. daily until sugar appears in the urine. Whenever this occurs, the diet may be halved or starvation instituted until the urine is sugar-free and the blood-sugar content normal. The patient may then receive the previous diet, except that the carbohydrate content must be reduced by approximately 33 per cent.

The subsequent course of treatment depends largely on the presence or absence of sugar in the urine, and the gain or loss of weight and strength. If the urine remains sugar-free and there is a steady loss of body weight below the desired level, the quantity of carbohydrate and fat in the diet must be increased. If faint traces of ketone acid are persistently present in the urine after sugar has disappeared and the maintenance diet has been established, there is usually no cause for concern. Such slight ketonuria usually disappears within a short time when the maintenance diet is properly apportioned and maintained. If it does not, and if the bicarbonate content of the blood is low, it is necessary either to lower the fat consumption by 20 to 100 gm., leave the quantity of protein constant, and increase the carbohydrate intake; or starve the patient completely for one to three days until the urine is free from diacetic acid.

Treatment With Insulin.—If glycosuria persists when the diet is such that it satisfies merely the minimal basal requirements, insulin must be given. Under such conditions, insulin therapy is more quickly and satisfactorily undertaken if the patient is immediately put upon a maintenance diet. The maintenance diet should be calculated on the basis of a requirement of between 1 and 1.5 gm. of protein per kilo for adults and 2.5 gm. per kilo for children. The carbohydrate intake should be equal to and seldom more than double the quantity of protein, and the fat consumption should be just sufficient to bring the total caloric intake to between 30 and 60 per cent. above the basal caloric requirement. When the diet has been thus established, insulin should be administered in the following doses: 5–20 units in the morning, fifteen to sixty minutes before breakfast, and 5–20 units, fifteen to thirty minutes before the evening meal, the actual dose depending, of course, on the degree of glycosuria. As long as glycosuria persists on such a régime, the dose of insulin should be increased 2 to 10 units every day or every other day, alternating the increase between morning and evening dose, until the urine is free from sugar both in the morning and at night. At this time mild symptoms of *hypoglycemia* often appear, usually in the forenoon or during the evening. When this happens it is necessary either to increase the carbohydrate 5 to 10 gm. or to lower the insulin dosage 2 to 10 units at the meal which precedes the development of hypoglycemic reactions. Proper adjustment of the carbohydrate consumption to the insulin dosage or vice versa, so that the symptoms of insulin reaction and glycosuria are both absent, may require weeks. It is much more difficult in children than in adults. As the effects of insulin are more transient in children, it may be necessary to administer four doses a day instead of two, the extra injections being made before the noon meal and late at night.

Hypoglycemic Reactions.—The symptoms resulting from an overdose of insulin are either sudden in onset (one to five minutes) or gradual, as, for example, five to twenty minutes. When the symptoms are sudden in onset they are usually also severe, *i. e.*, profound weakness sometimes with marked mental confusion, disorientation, diplopia, inco-ordination, fixed stare, sensory and motor aphasia, and unconsciousness with muscular tremblings which progress rapidly to convulsions (epileptiform in character). These convulsions which occur in "insulin reactions" or "insulin shocks" may in certain patients so closely simulate an epileptic convulsion both in their suddenness of onset and in their general characteristics that a

differentiation is possible only by means of blood-sugar determinations. The more usual manifestations of hypoglycemic reactions brought on by overdosage of insulin are general muscular weakness, momentary mental confusion, loss of memory, a sense of restlessness, profuse sweating, pallor or flushing of face, and trembling, "weak," and "hollow feeling" in the epigastrium—sometimes described as hunger. Sugar or orange juice or carbohydrate in any form usually allays these symptoms within five to twenty minutes; sometimes a non-caloric substance, such as hot broth, coffee, or tea will accomplish the same effect, but only temporarily.

Adrenalin in doses of 4 to 8 minims in children and 8 to 15 minims in adults serves to counteract the severe reactions temporarily, but should be immediately followed by adequate doses of carbohydrate, 5 to 20 gm., because the action of adrenalin is only transient and is not needed when the patient is sufficiently conscious to take carbohydrate by mouth.

Intravenous glucose is also useful in counteracting severe shock and may be given in concentrations as high as 50 per cent. (10 to 20 c.c.).

The milder symptoms of hypoglycemia may appear at blood-sugar levels of 0.08 to 0.07 per cent. Between the blood-sugar levels of 0.07 to 0.05 per cent., more severe symptoms, including diaphoresis and vertigo, are usually present, and below this level down to 0.035 per cent. the symptoms increase in severity until at the lower limit mentioned unconsciousness usually supervenes. The hypoglycemic reactions are more apt to be sudden in onset, severe, and prolonged in patients suffering from marked undernutrition. If untreated, severe hypoglycemic reactions may cause death, although this is an extremely rare occurrence.

Although it is possible under carefully controlled conditions to estimate the number of grams of carbohydrate which each unit of insulin can oxidize, the range of variation in different individuals (0.5 to 2.5 or even 8 gm. of glucose per unit of insulin) is so great that the dosage of insulin cannot be determined in this way. Diets which contain even more carbohydrate than that outlined above, *i. e.*, 200 to 400 gm., have been found practical and desirable for certain patients. In employing such diets, it is often surprising to find that the increase in the dose of insulin is not proportionate to the increase in the carbohydrate utilization, and that in some cases the original dose prevents glycosuria even when the carbohydrate intake is doubled.

Treatment of Chronic Acidosis.—Since acidosis results from the insufficient oxidation of the metabolic derivatives of fat, treatment should consist of measures to overcome this defect. *Brief periods of starvation* may be followed by administration of diets which contain little fat and sufficient carbohydrate to insure complete burning of the fatty acids without producing glycosuria. The glycosuria commonly associated with this type of mild or chronic acidosis usually disappears on the institution of a régime of undernutrition or when an adequate maintenance diet is given with insulin.

Treatment of Acute Acidosis.—The patient with acute acidosis requires *immediate treatment*. He must be put to bed at once and kept warm with blankets and hot water bags. The bowels should be emptied with an enema; cathartics are to be avoided. When the condition is acute, prompt treatment with insulin is indicated. The method of using insulin depends on the severity of the acidosis (degree of lowering of the blood CO_2)

and the clinical condition of the patient. If the acidosis is extreme (complete coma), insulin must be injected before any other therapeutic measures are taken; 50 to 75 units should be given subcutaneously and synchronously, 15 to 25 units intravenously. Thereafter, between 10 and 20 units of insulin given subcutaneously every hour or two is usually sufficient to combat the acidosis and reduce hyperglycemia. Unless there is need for the immediate action of insulin, intravenous administration of the hormone is inadvisable because a large part of the dose is probably eliminated through the kidneys before it materially affects the glucose metabolism. Since this hourly administration of the hormone must be discontinued as soon as the urine is sugar-free, specimens of urine should be taken and examined every hour or two. The blood-sugar content is an index of the balance between insulin dosage and the need for this medication. If it falls below 60 mgm. per 100 c.c., sugar must be administered promptly whether there are symptoms of *insulin shock* or not.

One of the most important parts of therapy is the *administration of fluid.* The extreme hyperglycemia and glycosuria lead to excessive diuresis and dessication of all the tissues with consequent concentration of the acid in the body fluids. When the patient is first seen, the acidosis is not usually severe enough to prevent ingestion of fluids, and even when the patient is partially or completely unconscious, fluid may be administered orally through a stomach tube. At least 200 c.c. should be given every hour by mouth or by hypodermoclysis. Orange juice or sugar dissolved in water should constitute a large part of the fluid given by mouth. A convenient empirical dose of glucose is 10 to 20 gm. every hour or two for the first ten or twelve hours. When it is impossible to administer carbohydrate by mouth because of nausea or vomiting, 10 to 20 per cent. glucose solution should be given by hypodermoclysis, in individual doses of 500 to 1000 c.c. If it is necessary to obtain an immediate effect, quantities not exceeding 500 c.c. in 10 to 50 per cent. solution may be injected intravenously. Sodium chlorid in physiological concentration should also be given by vein or by hypodermoclysis, so that from 7 to 10 gm. is administered every twenty-four hours. Gastric lavage is advocated by some practitioners.

On the assumption that acute acidosis is due, in part at least, to insufficiency of the total base content of the blood, 15 to 30 gm. (in the case of children, 5 to 15 gm.) of sodium bicarbonate should be administered in the first twenty-four hours. When there is no nausea or vomiting, 3 to 5 gm. may be given every hour in about 200 c.c. of water, until the reaction of the urine is neutral. The addition of small quantities of lemon juice makes this bicarbonate solution more palatable. If oral administration of alkali is impossible, a 5 per cent. solution of sodium bicarbonate must be injected intravenously. Great care is necessary to prevent escape of the fluid into the tissues. It is inadvisable to inject more than 500 c.c. at one time, and the administration of such large amounts should take at least three-quarters of an hour. The temperature of the solution must be slightly higher than that of the body. Symptoms of cardiac failure are combated by medication with digitalis and caffein, or by instillation of black coffee into the rectum.

After the acidosis has been overcome, efforts to maintain sufficient oxidation of glucose must be continued to prevent a recurrence. Consequently, the patient should receive at least 100 gm. of carbohydrate every

twenty-four hours, and if possible 50 to 70 gm. of protein, and 40 to 60 gm. of fat. This is a convenient and temporarily adequate diet which should be given for at least one to three days. The dosage of insulin depends in this stage on the presence or absence of glycosuria; usually administration of 10 to 20 units three times a day is sufficient, but the exact quantity needed and the time of giving varies in each individual. If the patient is going to continue to need insulin a maintenance diet may now be given.. When the severe form of acidosis has appeared in diabetes which is otherwise mild, because of infection or prolonged dietary abuse, it is desirable to reduce the insulin dosage gradually, lower the carbohydrate intake, and thus approach a maintenance diet low in carbohydrate, eventually aiming at the discontinuation of insulin. As the sugar and ketone bodies disappear from the urine, the subjective and objective symptoms of severe acidosis disappear, sometimes within six to twelve hours if prior to the giving of insulin, the coma has not existed for more than twelve to twenty-four hours, though at other times this takes much longer.

Diabetic Toxemia.—When symptoms of extreme acidosis have existed for more than thirty-six hours, or if complete coma has been present for more than twenty-four hours, the treatment already described is often without avail. The blood-sugar content may be decreased, glycosuria and ketonuria diminished, and the blood CO_2 restored to normal, but unconsciousness continues and the patient dies in what has been described as a state of diabetic toxemia. The coma of diabetic toxemia is unlike that of acidosis in that hyperpnea is absent. The dehydration has usually been overcome and the coma is like that of other non-diabetic toxemias.

Treatment of Ketosis.—Administration of insulin in the presence of adequate quantities of carbohydrate establishes a ketogenic-antiketogenic ratio which prevents the formation of ketone bodies and abolishes the existing hyperketonemia.

Treatment of Surgical Complications.—It is often necessary to operate on patients with diabetes. Before the discovery of insulin this was fraught with such risk that major operations were seldom performed. Since the discovery of insulin, however, surgical operations are not only possible, but safe, provided that adequate quantities of insulin and glucose are administered during the operative period. The schedule of treatment is to give 10 to 20 units of insulin with 10 to 20 gm. of glucose just before operation, and, at intervals of one or two hours after the operation, to administer 10 units of insulin with 10 to 20 gm. of glucose until the patient is able to eat (usually for twenty-four to forty-eight hours). The previous diabetic diet is then gradually resumed and sufficient insulin given to control glycosuria.

Personal Hygiene of Diabetic Patients.—A diabetic patient should lead an even, tranquil life, and be as free as possible from worry and excitement. In cold weather, warm clothes should be worn to conserve the body heat. As a rule, cold baths are to be avoided. Moderate exercise is desirable, but exhaustion must always be guarded against. For patients who are not vigorous enough for outdoor exercise, massage is useful. Individuals of middle age should give special care to the feet to reduce the danger of gangrene.

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DIABETES INSIPIDUS

Definition.—*Diabetes insipidus* is a chronic disease characterized by the passage of a large amount of very dilute but otherwise normal urine and by an enormous thirst.

Incidence.—It is a relatively rare condition which chiefly affects young people and is seen in males more frequently than in females. The importance of heredity has been well illustrated by the study of a number of interesting families, one of which (reported by Weil) included 23 victims of persistent polyuria among the 91 members of 4 generations. Gossage believed from his studies that *diabetes insipidus* was transmitted in the germ plasm as a dominant trait.

Symptoms.—There are two general groups of cases: (1) the so-called *primary*, or *idiopathic*, in which no organic disease is demonstrable, and (2) the *secondary*, or *symptomatic*, which is associated with an organic lesion of the brain or other parts. The lesions mainly associated with this second type are those produced by fracture of the base of the skull and other cranial injuries, basilar meningitis, especially of syphilitic origin, tumors of the brain, particularly those of the hypophysis and neighboring structures, cerebral hemorrhage, encephalitis, etc. There are also reports of its association with tumors and aneurysms within the abdomen and with tuberculous peritonitis. In cases of the *primary type* there may be no symptoms except those of the *diabetes insipidus* and at autopsy, no characteristic gross lesions except perhaps some enlargment and congestion of the kidneys, dilatation of the ureters, and hypertrophy of the bladder. In the secondary type the symptoms may be numerous and are those characteristic of the associated lesion.

The disease, which may be congenital, may begin suddenly after an injury, after an emotional shock, or after an infectious disease. Usually the onset is insidious, with gradually increasing polydipsia and polyuria. Trousseau's famous patient secreted 43 liters of urine in twenty-four hours and drank a corresponding quantity of fluid. It is said that one child passed a quantity of urine in one day the weight of which almost equaled that of the boy himself. Usual quantities vary from 8 to 12 liters in twenty-four hours. The *urine* is quite pale, almost colorless, of low specific gravity (1.001 to 1.005), and contains as a rule no abnormal elements. The *thirst*

is sometimes insatiable; or the satisfaction of it may be the greatest pleasure of life. When deprived of water the patients may suffer extremely, and under such circumstances they have been known to drink their own urine. It is easy to imagine the deleterious effects, especially on a nervous person, of the inconvenience, the embarrassment, the interference with daily activities, but particularly of the insomnia so often produced by the frequent necessity of arising at night to allay the thirst and to pass urine. Nevertheless, in some cases the general health is satisfactorily maintained and the patient may live with the disease for fifty years. The course of the secondary form of the disease depends upon that of the associated lesion and, as might be expected, the general health often fails rapidly.

With the marked polyuria there are evidences of a lack of fluid elsewhere in the body; the quantity of saliva is decreased, the skin is dry, there is no sweating, and constipation develops. While the concentration of the urine is very low, a normal amount of solids is passed in twenty-four hours. Increase of the nitrogenous food intake leads to increased output of nitrogen in the urine; and an increase of the chlorids in the diet also increases the quantity excreted, but with a great aggravation of the polyuria. When the fluid intake is restricted the specific gravity of the urine rises somewhat and the amount of urine diminishes, but not to normal. In most cases after the hypodermic injection of pituitrin the polydipsia and polyuria practically disappear, the concentration of the urine becomes normal, and all renal functional tests are normal. No significant metabolic disturbances have been demonstrated other than that of the water balance; and the delicate adjustment in the blood between solids and fluids and in the amount of dissolved substances is maintained as steadily as in health.

Pathogenesis.—In spite of much experimental work and great interest in the subject in recent years, the cause and the mechanism by which *diabetes insipidus* is produced are still obscure. A number of explanations have been suggested, among which may be mentioned: (1) a vasomotor disturbance of the renal vessels, due to local irritation (abdominal tumor), to central disturbance (brain lesion), or to functional irritation of the center in the brain; (2) diminished function of the posterior and intermediate portions of the hypophysis cerebri; (3) a physicochemical alteration in the tissues generally, which affects their capacity to store liquids and is mediated through a center in the *tuber cinereum*. In view of the recent demonstrations that the hypophysis may be completely removed without the production of this syndrome, that the phenomenon may be regularly produced by a small puncture in a limited area of the *tuber cinereum*, and that it may be induced in this way in animals whose kidneys have been denervated, current opinion in general favors the third explanation.

Diagnosis.—*Diabetes insipidus* is usually easily distinguished from *diabetes mellitus* by the glycosuria and the high specific gravity of the urine during the latter disease.

Hysterical polyuria may simulate *diabetes insipidus*. This primary polydipsia is, in most instances, transitory and there are usually other evidences of hysteria.

A large amount of urine of low specific gravity may be passed by some patients with chronic nephritis, but the presence of albumin and casts in the urine, the arterial hypertension, and the results of renal function tests should make the diagnosis easy.

Treatment should be based upon a thorough study of each case. In those associated with syphilis of the nervous system *antisyphilitic therapy* occasionally gives complete relief, but more usually improves the general health without greatly influencing the diabetes insipidus. In a few cases (presumably of the secondary, or symptomatic, type) complete cessation of the thirst and polyuria has followed *lumbar puncture.*

No attempt should be made to reduce the *amount of liquids* except perhaps in individual cases. The *diet* should contain only the minimal requirement of salt, but otherwise need not be restricted. Many *drugs* have been tried but, until recently, without any measure of success. It has now been demonstrated that regardless of the causation of the disease the hypodermic administration of *extracts of the hypophysis* (*pars posterior* and *pars intermedia*) exerts a remarkable effect. After a sufficient dose (which varies with individual patients) the concentration and quantity of urine becomes comparatively normal and the thirst disappears. Usually two or three injections of 1 c.c. of pituitrin each day are sufficient to secure comfort. This drug is invaluable in affording temporary relief, but the method of administration limits its usefulness. When administered by mouth or by rectum it has no effect. Blumgart reports that intranasal sprays and applications of the preparation are effective when used in much larger doses than those which bring relief after hypodermic injection.

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LIPOMATOSIS

Definition.—Various observers have described a number of different types of localized or unusual deposition of fat, all of which may be grouped under the term "lipomatosis" to distinguish them from the ordinary form of obesity. Lyon has pointed out the transitions between types, and considers them not clinical entities, but variations of a common morbid process.

Clinical Types.—(1) *Nodular, Circumscribed Lipomatosis.*—Single or multiple encapsulated lipomata are very common, vary greatly in size, and affect women more frequently than men. They are soft and lobulated as a rule, and although they usually cause no symptoms may be tender or even spontaneously painful. When very numerous or very unfortunately situated they may cause mechanical interference with normal functions.

(2) *Diffuse Symmetrical Lipomatosis* (Fetthals; Adenolipomatosis).—In diffuse symmetrical lipomatosis the fatty masses are not encapsulated; they are more common in men than in women, may be of very large size, and very disfiguring. The term "fat neck" appropriately indicates the

marked predilection for this region. Huge masses may cover the shoulders and extend down the arms or may be arranged in segmental fashion on the thorax. Sometimes there is a remarkable localization in regions rich in lymph-glands, so that at first sight a disease of these structures is suggested. Lymphoid tissue or hemolymph-nodes may be found in the masses, but are no more characteristic of this type than of the other forms of lipomatosis. Although symptoms are usually absent, those more characteristic of Dercum's syndrome may be present.

(3) *Adiposis Dolorosa, or Dercum's Disease.*—The cardinal features of *adiposis dolorosa* are fat deposits, pain, asthenia, and psychic manifestations. The condition is much more common in women than in men, and is apt to occur in fat neuropathic individuals at the time of the menopause. Spontaneously painful, very tender, irregular deposits may appear in the subcutaneous fatty tissues. On palpation they may resemble a "caking breast" or feel as though "filled with a bundle of worms." Asthenia is usually a striking feature. "Rheumatic" pains appear in muscles and joints. The onset is insidious. Exacerbations and remissions occur, but the symptoms usually persist to some extent.

(4) *Adipositas Cerebralis.*—Under the heading of *adipositas cerebralis* may be grouped all disturbances due to intracranial lesions or associated with a deficient functioning of the hypophysis. The *dystrophia adiposogenitalis* of Fröhlich (1901) is the classical example. The symptoms of such cases with a gross lesion, usually a tumor, of the hypophysis or neighboring structures may be

1. Due to the brain tumor:
   (*a*) General symptoms of increased intracranial pressure; headache, vomiting, etc.
   (*b*) Neighborhood symptoms due to local pressure; visual disturbances, hemianopsia, optic atrophy, changes in the sella turcica.
2. Referable to the loss of hypophyseal function(?); adiposity, genital dystrophy; perhaps polyuria, etc.

(5) *The Lipomatosis of the Pseudohypertrophic Form of Muscular Dystrophy.*—In lipomatosis of the pseudohypertrophic form of muscular dystrophy the dystrophic muscle groups may be strikingly enlarged by marked infiltration of adipose tissue between the muscle bundles. There may also be unusual fatty deposits in the mammary and inguinal regions.

(6) *Lipodystrophia progressiva*, a rare condition in its fully developed form, begins in childhood and affects girls almost exclusively. It is characterized by a sadly disfiguring emaciation of the upper portion of the body with a remarkably complete disappearance of subcutaneous fat and by a grotesque obesity of the lower half of the body. The general health may be good, but there are often psychoneurotic symptoms.

Morbid Anatomy.—At autopsy in cases of lipomatosis the associated lesions of other structures, especially of the endocrine glands, are of considerable interest, but the variety of the lesions even in cases belonging to the same clinical group prevents any clear understanding of the relationship. Even in *dystrophia adiposogenitalis* different structures have been affected and some disturbances have been attributed to primary gonadal changes. In Dercum's disease pituitary tumors have been found as well as thyroid changes. Marine believes that atrophy of the thyroid is the characteristic

lesion. Degenerative changes in the peripheral nerves have been noted and may account for some of the symptoms.

It is universally recognized that these fatty peculiarities are of endogenous origin, but there is question as to whether they are due to disturbances in hormones (internal secretions), to changes in the nervous stimuli, or depend upon powers inherent in the cells of the subcutaneous tissue. Each theory has its advocates and it may be that all three are in some way combined.

Treatment, except when the fatty masses may be removed by operation, is unsatisfactory. Small doses of dried *thyroid* or of *thyroxin* may be of value in *adiposis dolorosa* and whenever the metabolic rate is retarded. *Pituitary extracts* may be tried in appropriate cases. "*Leptynol*" is a German preparation of palladium in lanolin for local injection into fatty masses. The *dietetic-hygienic regimen* should be adapted to the state of general nutrition.

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HEMOCHROMATOSIS

Definition.—*Hemochromatosis*, or *bronze diabetes*, is a disease of metabolism characterized by a marked *deposition of pigments*, especially the iron-containing hemosiderin, in many organs of the body; by *cirrhosis*, particularly of the liver and pancreas; and in most cases by *diabetes*.

Incidence.—Less than 100 cases have been reported, and only very few of them in women. The disease attacks middle-aged men, but, though symptoms begin at this time of life, it is probable that the pathological process originates many years earlier.

Etiology.—The cause of hemachromatosis is not understood. There is difference of opinion concerning the relationship of the pigmentation and of the cirrhosis to each other. The earlier belief that the pigment deposit was caused by increased destruction of blood is no longer accepted. Similar pigmentation has been described, by Rous, in rabbits which had destroyed transfused blood constantly for many months, and by Mallory, in animals poisoned by copper salts. There is a marked retention of iron in the body, as much as 40 gm., ten times the normal amount, and, as it seems from metabolism experiments that the retention is not complete, many years must be required for its accumulation. The diabetes is generally attributed to the pancreatic lesion.

Morbid Anatomy.—At autopsy the enlarged, cirrhotic liver, the pancreas, and the lymph-nodes draining these organs are of a striking ochre color. Other glandular organs show relatively slight macroscopical pigmentation. Histologically, hemosiderin is found in large amounts in the liver, pancreas, and lymph-nodes, and in smaller amounts in the other important glandular

structures as well as in the spleen, the heart muscle, and, in some cases, in the capillary endothelial cells of the skin and of the genito-urinary tract. Hemofuscin, a finely divided, light yellow pigment, which does not contain iron, may be found in connective-tissue and smooth muscle cells. Physiological pigments are increased.

Symptoms.—The early symptoms may be those of diabetes. In other cases the *onset* is insidious, with asthenia and malaise; or sometimes a complication, such as tuberculous peritonitis, may be the first manifestation.

The *skin pigmentation* in well-marked instances has a distinct bronze shade and in extreme cases may even be bluish black. The mucous membranes are usually not pigmented. The *liver* is enlarged and may be tender. The *spleen* is usually palpable and firm. There is no *jaundice* and no characteristic change in the blood beyond the *slight secondary anemia* so frequent in chronic disease. Rous reports the finding of easily recognizable *hemosiderin in the urinary sediment* in hemochromatosis and in pernicious anemia, and this test may prove to be a valuable clinical aid. Careful controls with other urinary sediments should be made at each examination with freshly prepared solutions of potassium ferrocyanid or of ammonium sulphid. The diabetes is usually severe.

Diagnosis.—A diagnosis of hemochromatosis is suggested by the association of asthenia, malaise, skin pigmentation, enlargement of the liver, and palpability of the spleen, with or without diabetes. It may be confirmed by the finding of hemosiderin in the urinary sediment or in a section of excised skin.

Prognosis.—The prognosis is unfavorable. After symptoms appear the disease lasts only a few months or, at best, a few years.

Treatment must be symptomatic, since our knowledge does not permit rational etiological therapy. The diabetes should be treated like the ordinary type of *diabetes mellitus*.

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OCHRONOSIS

Definition.—Ochronosis is a rare metabolic pigmentary disorder which results in darkening of the cartilages and certain of the fibrous tissues and in pigmentation of the skin. Degenerative cartilaginous changes may develop into arthropathies.

Incidence.—There have been reported between 40 and 50 cases which may be divided into three groups: (1) Those associated with alcaptonuria, a constitutional, familial anomaly of the metabolism of the aromatic amino-

acids which is manifested by the excretion in the urine of homogentisic acid, normally an intermediary product of amino-acid catabolism. Such urine turns brown on standing or after the addition of alkali. (2) Those associated with the prolonged use of carbolic acid applications. (3) A smaller group, in some of which melanin instead of homogentisic acid may be found in the urine. Ochronosis is more frequent in men than in women and usually affects older people.

Morbid Anatomy.—The most heavily pigmented structures, the cartilages of the ears, trachea, bronchi, ribs, intervertebral disks, and symphysis, are dark gray or black. Those most involved become degenerated and worn and there is new bone formation (osteo-arthritis). The pigment is apparently a melanin and appears microscopically as finely divided yellowish-brown granules or else colors the tissue diffusely.

Etiology.—The etiology of the disturbance is not thoroughly understood, but in all cases there is doubtless a large constitutional (probably inherited) factor. Most alcaptonurics do not show ochronosis, and consequently the causes of the two conditions cannot be exactly the same. It is generally believed that melanin is formed from proteins through the aromatic amino-acids, probably through the activity of tyrosinase.

Symptoms.—There may be no symptoms. The earliest manifestations consist of a bluish coloration of the ear cartilages, black flecks or streaks in the scleræ, and slight pigmentation of the skin of the face. In advanced cases there is marked skin pigmentation, discoloration of the tendons of hands and feet, greenish-brown axillary sebum, a brownish-black cerumen, and usually an osteo-arthritis, especially of the larger joints. The urine, of course, should be carefully examined.

Treatment.—Careful search should be made for any possible extrinsic cause, such as the use of carbolic acid or exposure to similar chemicals. Attempts may be made to reduce the exogenous protein component by reducing the dietary protein to the minimum, 0.7 to 0.8 gm. per kg. of body weight, and selecting proteins of low tyrosin and phenylalanin content. The joint symptoms may be treated as in other types of osteo-arthritis.

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OBESITY

Definition.—Obesity is a state in which the amount of fat stored in the body is excessive.

Incidence.—Obesity is one of the commonest ailments to which the flesh is heir, and is of importance to the individual in proportion to its degree and its association with other diseases. To the community it is of importance in that it may *per se* decrease human efficiency and shorten human life. The latter is proved conclusively by the data of life insurance companies.

Etiology.—The fundamental cause of obesity is a positive energy balance. That is, the calorific value of food absorbed is greater than the total expenditure of energy. A comparatively slight disproportion between fuel intake and combustion may, over a period of years, result in a marked grade of obesity. Thus von Noorden calculates that an excess of but 200 calories a day will in the course of a year lead to a gain in weight of 24 pounds. Indeed, the extraordinary thing is not that so many persons become obese, but rather that more do not. Most persons preserve a constant and normal weight in spite of marked variations in their bodily activity and without conscious regulation of their food intake. This is because the normal appetite ordinarily adjusts intake so accurately that it just meets, but does not exceed, the requirements of energy expenditure. When this adjustment loses its delicacy and eating falls under the rule of habit, obesity may develop.

Morbid Physiology.—Obesity has been divided into two main types—endogenous and exogenous. In the former, there is an actual slowing of oxidative processes; in the latter, the general rate of metabolism is normal. The endogenous variety is due, probably invariably, to abnormalities in the function of one or more of the endocrine glands and is discussed elsewhere in this volume under that heading. In passing may be mentioned the obesity associated with myxedema, with hypopituitarism (Fröhlich's syndrome or *dystrophia adiposogenitalis*), and with dystrophies of the gonads. A much greater proportion of obese persons belong to the exogenous group.

That no fundamental alteration in rate of combustion exists in simple or exogenous obesity is amply proved by studies of the so-called basal metabolic rate. For example, using the DuBois standards, a series of 41 obese persons studied at the Massachusetts General Hospital showed an average variation from the expected metabolism of but 0.5 per cent. Similar results have been obtained by others.

Nevertheless, it is a matter of common belief that certain persons tend to gain weight while others *apparently* eating as much and exercising no more do not. The explanation of this is not to be found in the kind of food ingested. The ratio between total calory intake and total calory output is what counts. All excess calories, after the glycogen depots are filled, are stored in the body in the form of fat whether they were originally derived from fat, protein, or carbohydrate. Differences in energy reaction to similar stimuli may explain some of the differences in the tendency to gain weight. While the basal metabolic rate of an individual who gains weight readily may be the same as that of one who does not, their total metabolisms may be different, and it is the total metabolism in relation to fuel intake which determines weight behavior. The performance of muscular work and the ingestion of food accelerate metabolism; so do emotional disturbances, probably through the liberation of adrenalin. Total metabolism consists in basal metabolism plus the increments due to all these causes. It is entirely possible that the individual who gains weight readily reacts less intensively to such stimuli than one who has no such tendency. In the former the total metabolism would be less than in the latter, even though the basal rate of the two were the same.

For the most part clinical experience bears out such an hypothesis. Individuals who gain weight readily, even though they apparently do not eat

to excess, are usually phlegmatic; they worry less, sleep either longer or more soundly, and when at rest relax more completely than persons of the normal or thin types.

Morbid Anatomy.—In the milder grades of obesity there is simply an excess of fat in the normal fat depots, such as the subcutaneous and retroperitoneal tissues, the breasts, and the omentum. In the severer grades, fat infiltration is found also in parenchymatous organs such as the heart and liver.

Symptoms.—Slight degrees of obesity cause no symptoms. As adiposity increases, the extra weight, of itself, gives rise to a certain amount of dyspnea on exertion and perhaps to increased tendency to fatigue. When the obesity becomes extreme, the state of corpulence alone may lead to mechanical limitations, finally ending in nearly complete incapacity. The symptomatology of obesity is, however, most conspicuously of an indirect variety. The added burden of fat puts the whole body under the strain of extra work which manifests itself in an exaggeration of the symptoms due to any co-existing morbid tendency. As a recent writer has well put it, "fat is a parasite." The patient suffers chiefly from the effect of his obesity upon his other bodily weaknesses. Thus the cardiac patient who becomes obese is in increased danger of cardiac failure, and the kidneys, pancreas, and liver of the obese carry an abnormal load. It is generally conceded that obesity predisposes to diabetes, and it is also true that often the obese have moderate arterial hypertension, which tends to decrease when their weight is reduced.

Diagnosis.—Inspection gives the diagnosis. The determination of cause is the important thing. The habits of eating and exercise should be investigated and an attempt made to discover whether the cause lies in excessive food intake, insufficient exercise, or both. Upon such an evaluation will depend the success of treatment. The existence of endocrine factors must also be determined. There are many borderline cases not frankly endocrine, yet with some endocrine element. Metabolism studies aid in the recognition of these. In thyrogenous obesity the basal metabolic rate is invariably decreased. In pituitary obesities, according to the recent literature, the basal rate may be normal, but the increase following protein ingestion (the so-called specific dynamic action of protein) may be less than normal.

Prognosis.—The prognosis depends upon such factors as the grade of obesity, the willingness of the patient to reduce, the extent of endocrine involvement, and the complications. Acute infections, particularly pneumonia, cardiac and renal lesions are more serious in the obese, particularly in the very obese, than in otherwise normal persons. Complications are of importance also in connection with the possibility of reduction, in so far as they interfere with the inauguration of therapeusis. Not only is a given cardiac lesion of worse prognostic significance in the obese, but through the limitation it imposes upon bodily activity it also diminishes the chance for successful reduction.

Treatment.—*Prophylaxis* is better than treatment. It is easier to prevent obesity than to cure it. The family physician should encourage patients to weigh themselves and keep their waist measure from increasing. The treatment of simple or exogenous obesity lies in the correction of the disproportion between the intake and expenditure of energy. To that end we may restrict food consumption and increase bodily activity. The

treatment is, therefore, essentially dietetic and hygienic. Drugs are indicated for the complications only. Massage and hydrotherapy are often important adjuncts, particularly in patients who for any reason cannot take active exercise. For success in treatment the patient's co-operation is essential. No one can be satisfactorily reduced who does not wish to be. It should be remembered that most fat persons, though they may not admit it, take delight in eating. Food intake with them has fallen under the head of habit instead of instinct. With the physician's help the habit can be gradually broken and the patient be satisfied with an adequate instead of an excessive amount of food. In women, a desire to reduce often springs from vanity, and in either sex this desire may be stimulated by a thorough explanation of the dangers of corpulence.

The indications for a reduction cure depend on several factors, such as the patient's age (reduction cures are undesirable in the elderly), the degree of obesity, and the existence of complications. In the slightly overweight otherwise healthy subject the indication may be for the regulation of diet and exercise only to the point of preventing further gain. Sometimes the forbidding of candy alone, or of excess butter, cream, sugar, or bread will accomplish this. In the somewhat more obese, but still otherwise healthy patient, the regulation must be more strict and a loss of weight sought. The physician must follow his patient until the desired reduction has been achieved and thereafter guard against a recurrence. He must decide upon the desirable amount and rate of loss in weight. In the former he will be guided by standard figures for the weight of normal persons, but will usually want to carry the reduction only part way toward these standards. The rate of reduction in simple obesity should be slow. The fat accumulation of years cannot be got rid of in a few weeks as some patients seem to expect. Ordinarily from 2 to 5 pounds loss per month is sufficient. In cases where the desired reduction is a matter of only 10 to 20 pounds the rate of loss may be made very slow indeed. The slower the loss, the easier it is to establish the patient permanently on a diet which will prevent recurrence of his obesity.

A variety of reduction diets has been proposed. None possesses any unique virtue. The dietetic indication is simply to decrease total fuel intake without destroying the proper balance of the ration or depriving the body of vitamins. The amount of protein allowed may be liberal and never should be reduced below 70 to 80 gm. A restriction below that might lead to the destruction of body protein, thus weakening the patient. The restriction should be chiefly in fats and the concentrated carbohydrate foods, sugar, and breadstuffs. Fruits and the low carbohydrate vegetables are invaluable since through their bulk they not only reduce the pangs of hunger but also supply certain vitamins. The physician with the use of food tables must plan the diet to meet the requirements of the individual patient. His customary caloric intake must be estimated, and at first the effect of a 20 per cent. restriction may be tried. If the weekly weighings, which should invariably be made, do not show the desired weight loss, a 40 per cent. or 60 per cent. or even greater restriction may be necessary. For a time at least, except when the amount of weight to be lost is slight, the patient should be required to weigh his food. Better co-operation will be secured if, in the selection of foods, the likes and dislikes of the patient are considered as far as possible. A program of gradually increasing exercise

should be combined with diet restriction. Prolonged and gentle exercises are better than short violent ones. The latter are likely to increase the appetite and so defeat the object in view.

In extreme obesity, especially with cardiovascular disease, a rapid reduction may be necessary for a short time. In obese cardiac patients with congestive failure a diet of 800 to 1000 c.c. of milk alone (Karrell) may be very valuable for periods of one to two weeks at a time. Diets of 900 to 1200 calories per day with 60 gm. of protein may be kept up for somewhat longer periods.

Probably the only drug which directly causes loss of weight is thyroid. It brings about reduction through the acceleration of metabolism, in other words, by producing hyperthyroidism. It corrects one evil by creating another. In the opinion of the writer it never should be used in the treatment of exogenous obesity, except in extreme grades, with complications demanding rapid reduction. For such a purpose Mason, at the Royal Victoria Hospital in Montreal, has used thyroid successfully in combination with partial starvation. His patients, however, were under constant observation, so that the ill effects of the drug could be guarded against. Only under such carefully controlled circumstances should it ever be used in non-hypothyroid patients.

The treatment of *endogenous* obesity is that of the exogenous type plus, perhaps, certain organotherapy. For the obesity of hypothyroidism, thyroid substance is a specific. In pituitary obesity, pituitary substance has occasionally brought success; while gonadal substance in the obesities accompanying gonadal dystrophies has proved disappointing.

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Note.—Food tables will be found in "Food Values," E. A. Locke. Tables of average weight of normal men and women will be found in the second reference of the above list.

ACIDOSIS

Definition.—"Acidosis" is the term usually employed to designate a reduction of the bicarbonates (alkaline reserve) in the blood below the normal level.

Blood is a complex buffer solution. A buffer solution is one to which considerable amounts of acid or alkali may be added with a minimum change in reaction (hydrogen-ion concentration.) The chief constituents of the blood contributing to its buffer qualities are the proteins, hemoglobin, bicarbonates, phosphates, carbonic acid, chlorids, free oxygen, and ammonium salts. Of greatest importance clinically, however, are the bicarbonates. Normally, the concentration of bicarbonate is about 0.03 molar, and is usually estimated and reported as the amount of CO_2 per 100 c.c. of blood, which the bicarbonates contain. The normal variation of the blood CO_2 is between 55 and 65 volumes per cent.

A less common use of the term "acidosis" is in connection with an *increase in the hydrogen-ion concentration* of the blood above the normal range. The reaction (hydrogen-ion concentration) of the blood depends not so much on the concentration of the bicarbonates and other buffer substances, as on the relative amounts or ratio of weakly dissociated acids and their bases. Blood reaction is customarily reported as the logarithm of the actual value of the hydrogen-ion concentration, using the notation *p*H. The normal *p*H range is between 7.35 and 7.45. Since the acid-base ratio is the important factor in maintaining a hydrogen-ion concentration within very narrow limits in order that the life of the cells may not be endangered, the expression "acid-base equilibrium" is frequently used in connection with the reaction of the blood and body fluids.

The distinction between a reduction in the bicarbonates and an increase in the hydrogen-ion concentration of the blood should be clear. It is quite possible to have a markedly reduced bicarbonate concentration and a normal *p*H, in fact, this is frequently the case. Conversely, the bicarbonate of the blood may be normal, or even increased in amounts, and the reaction of the blood be more acid than normal. It is true, however, that decreasing the buffer substances, such as the bicarbonates, markedly reduces the efficiency of blood as a buffer solution, and therefore increases the tendency to a disturbed ratio between acid and base, resulting in a more acid reaction.

Under average normal conditions of activity and food intake the acid waste products of metabolism are in excess of the basic. The mechanisms for coping with this contingency are: (1) the buffer quality of the blood which maintains a constant reaction, chiefly by combining the acid radicles with the base of the bicarbonate, the liberated CO_2 passing off through the lungs; (2) the excretion by the kidney of a urine much more acid than blood, and the consequent return of base to the body to form bicarbonate ready for transporting more acid to the kidney; and (3) the utilization of ammonia to combine with acid radicles to be eliminated as neutral salts.

Occurrence.—Whenever the intake or production of acid exceeds the capacity of the regulatory mechanism, acidosis results. In normal circumstances the regulatory mechanism encounters no difficulty from food intake and the products of metabolism. Experimentally, it is quite possible to overtax the mechanism by the ingestion of acid. The most common cause of acidosis is the excessive production of beta-hydroxybutyric and acetoacetic acids by faulty fat and protein metabolism. Less frequently other organic acids may be produced in amounts sufficient to produce an acidosis.

In the event of a derangement of the regulatory mechanism conditions of acidosis may arise as the result of the retention of acid radicles. Disease of the kidneys may lead to a retention of phosphoric acid and a reduced

capacity to utilize ammonia in the excretion of acid radicles. In diseases of the lungs the elimination of CO_2 may be interfered with until CO_2 accumulates in the blood and increases its *p*H.

So far as is known at present acidosis is of clinical importance only if severe. Varying grades of acidosis may appear in a variety of diseases; in a few it is of considerable significance. The more important conditions in which acidosis may be present are:

Diabetes Mellitus.—Acidosis is one of the most serious features of *diabetes mellitus;* in fact, it is usually the cause of death. Owing to the inability on the part of the diabetic to burn glucose the oxidation of fat and certain amino-acids does not proceed beyond the oxybutyric and diacetic acid stage. A production of 100 grams of beta-hydroxybutyric acid in twenty-four hours has been reported.

Childhood.—Cyclic vomiting in children is often associated with the production of large amounts of ketone bodies and a marked lowering of the alkaline reserve. A disturbance in the metabolism of fat and proteins may occur quite suddenly in a perfectly healthy child. The production of ketone bodies may be considerable and the acidosis extremely grave. This condition is usually accompanied by gastro-intestinal symptoms, vomiting, diarrhea, and slight fever. In the diarrheal diseases of children marked acidosis may be due to either the production of excessive amounts of an unidentified acid or the loss of base through the bowel.

Renal Disease.—In the terminal stages of chronic nephritis a very marked lowering of the bicarbonate of the blood is occasionally observed. Less frequently, acidosis is encountered in acute nephritis.

Infectious Diseases.—A marked lowering of the bicarbonate content of the blood is seldom observed in the infectious diseases. In pneumonia there is occasionally an increase in the hydrogen-ion concentration. Mild grades of acidosis may obtain in any of the infectious diseases, more especially during the course of rheumatic fever, pneumonia, typhoid fever, and generalized tuberculosis. Dangerous acidosis occurs in Asiatic cholera.

Starvation.—For three to five days after the initiation of a fast large quantities of the ketone bodies may be produced. In certain individuals, usually obese, an acidosis sufficient to cause headache, lassitude, and nausea may develop. Fatal acidosis as the result of starvation alone in normal persons has not been reported.

Anesthesia.—Usually acidosis is only slight during anesthesia. Occasionally the condition may be serious in critical cases.

Pregnancy.—Mild grades of acidosis have been reported during pregnancy.

Chronic Disease.—Moderate degrees of acidosis are associated with pernicious anemia, cirrhosis of the liver, cancer, and other wasting diseases.

Poisoning.—Intoxication with methyl alcohol, salicylates, and carbon monoxid also causes acidosis.

Trauma.—Traumatic shock and severe burns often establish the condition.

Diagnosis.—Only marked acidosis can be recognized clinically. The patients complain of headache, weakness, drowsiness, and eventually become hyperpneic. The characteristic fruity odor of the breath due to the excessive production of ketone acids may frequently be noted. There are few conditions in which laboratory tests are of greater service than in

the diagnosis of acidosis. The information thus obtained is most useful when there is a distinct lowering of the alkalin reserve which is still insufficient to produce clinical symptoms. Early recognition of this frequently makes it possible to prevent serious acidosis.

The most useful and reliable test is the *determination of the CO_2 combining power of the plasma* according to the method of Van Slyke. As mentioned earlier, the normal range is 55 to 65 volumes per cent. Values between 40 and 55 volumes per cent. are indicative of mild acidosis. The range between 30 and 40 volumes per cent. is important. While not in itself dangerous, it represents the stage immediately before clinical symptoms appear and is the period when wise therapy may prevent a more serious condition. Hyperpnea, headache, weakness, and general malaise almost always are felt when the CO_2 combining power is in the neighborhood of 30 volumes per cent. As the blood CO_2 diminishes, the hyperpnea becomes greater and the drowsiness increases until deep coma supervenes at about 18 to 20 volumes per cent. While patients may recover after the alkaline reserve has been reduced to 10 volumes per cent., this level is extremely critical. The author has seen recovery when the combining power had been reduced to even 8 volumes per cent.

There are several methods for estimating, either directly or indirectly, the degree of diminution of *alkaline reserve*. They are, however, not so satisfactory as the estimation of the blood CO_2. A description of the several methods may be found in Van Slyke's articles on the subject.

So far as is known at present an increase in the hydrogen-ion concentration of the blood without a lowering of the alkaline reserve is of secondary clinical importance. An increase in the *p*H of the blood can only be determined by laboratory means, the simplest of which, and at the same time fairly satisfactory, is the colorimetric method of Cullen and Van Slyke.

Prognosis.—That acidosis is an abnormal physiological state, which may appear in a variety of pathological conditions, and *not a disease,* should be clearly appreciated. The prognosis, then, depends to a considerable degree on the underlying cause. Prognosis should be guarded in any case with clinical manifestations, for the more marked the clinical signs and the lower the blood CO_2 the greater the danger to the patient. An important factor in prognosis is the response to treatment.

Treatment.—Of great importance is the treatment of the disease which causes acidosis. It is safe to consider acidosis a "symptom" from which the patient needs prompt relief, and care should be taken to prevent any recurrence of the condition. When acidosis is due to the production of large amounts of ketone bodies (beta-hydroxybutyric acid, diacetic acid, and acetone) the immediate fundamental fault is in the oxidation of fat, and may depend upon lack of sufficient glucose to burn the fatty acids completely or non-utilization of glucose. In *diabetes mellitus* glucose is not burned and an excessive amount of the ketone acids is produced; hence elimination of the fats and a reduction of the protein in the diet is indicated. The discovery of insulin has quite revolutionized the treatment of acidosis in diabetes, so that, added to the dietary measures, we have a means of greatly reducing the mortality from acidosis in this disease. Conditions other than diabetes in which excessive amounts of the ketone acids are produced are usually caused by insufficient intake of carbohydrates; they should be treated by administration of more carbohydrate by mouth, rectum, or

subcutaneously, intravenously, or intraperitoneally, as the case may warrant. Much may be accomplished in preventing the acidosis of anesthesia and the acute infections by the administration of water, carbohydrate, and alkalies before operation, and thereafter if necessary.

Less is known about the acidosis which may result from the production of abnormally large amounts of acids other than beta-hydroxybutyric acid. In methyl alcohol poisoning the offending acid is formic acid, the oxidation product of methyl alcohol.

Acidosis occurring in renal diseases may be prevented or combated by giving a diet containing little protein and cereal and many vegetables, fruits, and nuts, supplemented by moderate amounts of sodium bicarbonate by mouth.

Conditions with an increased hydrogen-ion concentration without a reduction in the blood bicarbonate are best treated by caring for the underlying disease. In respiratory diseases, in which this complication is most frequently encountered, the use of oxygen to facilitate gaseous exchange is of value.

General measures, such as forcing fluids, establishing good elimination through the bowel, and keeping the patient warm, should always be employed against acidosis. In most instances this is inadequate. When the acidosis is severe (when the blood CO_2 is below 20 volumes per cent.) it is usually safer to give slowly 500 mils. of a 5 per cent. sodium bicarbonate solution intravenously. Sodium bicarbonate solutions for intravenous use should be prepared with normal saline, and be sterilized by boiling ten minutes, or autoclaving at 20 pounds pressure for fifteen minutes. This procedure converts some of the bicarbonate into carbonate. (Formerly sterile CO_2 was bubbled through the solution to insure a pure bicarbonate content. This is not necessary.) This treatment may tide over a very critical stage before the underlying process is under control. In milder conditions sodium bicarbonate may be given by mouth in 2- to 5-gm. doses, but not oftener than every hour. It is unwise to give large amounts of sodium bicarbonate by mouth, rectum, or vein without controlling the effect on the blood CO_2. As soon as the plasma CO_2 has reached its normal level all that can be gained by administration of alkali has been accomplished, and this treatment should be discontinued. Forced injection of alkali beyond this point is fraught with danger. A less reliable means of controlling the administration of alkali is through the reaction of the urine. Administration should be discontinued as soon as an alkaline or neutral reaction to phenolphthalein is obtained or, better still, as soon as an appreciable effect on the hydrogen-ion concentration is evident.

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ALKALOSIS

Definition.—Alkalosis is an excessive alkaline reaction of the body fluids. It is not a disease entity in itself, but designates a change from the normal state,—a disturbance of the acid-base balance toward the alkaline side. The means by which the acid-base relation is maintained, such as the "buffer

substances," the sodium bicarbonate and carbon dioxid ratio, the respiratory and kidney functions, have been discussed in the article on Acidosis (p. 597). Alkalosis may be produced by an absolute or relative alkali increase. An absolute increase usually comes from ingestion of alkalis and their organic salts beyond the amount that the body can neutralize and excrete. In a salt of an alkaline metal and an organic acid, such as sodium citrate, the acid radicle may be oxidized to carbon dioxid and water and the alkali left in the body tissues or fluids. A relative alkalosis accompanies rapid or excessive loss of acid radicles and the body is unable to compensate for this loss. Acid radicles, especially carbon dioxid, may be lost from the lungs by overventilation, which is a deep and rapid breathing. Likewise from the stomach, the hydrochloric acid may be lost by vomiting or very severe diarrhea.

Clinical alkalosis is practically always due to (1) alkali ingestion, (2) loss of carbon dioxid, (3) loss of hydrochloric acid. The alkali ingestion is usually some form of alkali therapy. The loss of carbon dioxid by overventilation may be voluntary, hysterical, or may result from a central nervous system lesion,—traumatic or irritative condition of the respiratory center. Diseases of the gastro-intestinal tract, such as pyloric or high intestinal obstruction, ventral or diaphragmatic herniæ, a marked gastritis, etc., may cause such frequent vomiting with such a marked loss of hydrochloric acid that the state of alkalosis is produced. Vomiting from brain lesions, toxemias and pregnancy, can have the same effect.

Regardless of the mechanism that produces the condition, the signs and symptoms of the alkalosis are usually the same. They are essentially the signs and symptoms of tetany which have been described under that heading (p. 1138). As in tetany, they may be so mild as to escape notice, or there may be marked restlessness, excitability, tingling, pricking sensations and numbness, usually of the extremities and face, tremor of eyelids, followed by tetany and convulsions. The facial muscles may be tense and show tremor. Chvostek's and Trousseau's signs are often present. There is an increased irritability of the neuromuscular apparatus to mechanical and electrical stimuli. The alveolar carbon dioxid is increased in alkali excess, decreased in carbon dioxid and hydrochloric acid deficit. The carbon dioxid combining power of the blood is increased to 70 volumes per cent. or more. The blood chlorids are low, especially with hydrochloric acid loss. The urine is alkaline and often shows marked effervescence on addition of acid.

The recognition of the condition of alkalosis is important because, as a complicating factor in a diseased state, it is a serious embarrassment to comfort, to treatment, and even to life. It is important to realize that a patient may have acetone in the urine and still be in alkalosis. It must be remembered that only a small amount of alkali may change the state of a patient from acidosis to alkalosis. This is often found when the kidney function has been impaired by poisons, such as bichlorid of mercury, and in chronic nephritis. In these conditions the "buffer" effect of the body fluids is at a low level and the kidney function has been impaired so that the excess base or acid cannot be excreted. In such cases the carbon dioxid combining power may be very low even when the symptoms of alkalosis are present.

Treatment.—The treatment depends on the causative factors. The underlying disease and its symptoms are a great help in determining the

mechanism of the change to an excessive alkaline reaction. If there has been alkaline treatment, this should be stopped and dilute hydrochloric acid given. If there has been a "blowing-off" of carbon dioxid by deep breathing, efforts should be made to prevent this. If the explanation to a patient of the necessity of breathing more slowly and less deeply fail, mechanical means to increase the carbon dioxid in the inspired air should be employed. This may be done by increasing the dead space of the respiratory tract, as by a gas mask, by breathing through a large tube a foot or more long, by rebreathing into a gas bag, or by giving carbon dioxid-oxygen mixtures. In conditions where there has been loss of hydrochloric acid, dilute hydrochloric acid should be given to lower the alkalinity and to increase the chlorids in the system. If hydrochloric acid cannot be given by mouth, 200 to 500 c.c. of ammonium chlorid in isotonic solution, 8 to 9 grams to the liter, may be given by vein. All therapy by mouth or vein should be given slowly and cautiously, as too rapid, too abrupt, or too marked changes are not desirable.

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DISEASES OF THE DIGESTIVE SYSTEM

DISEASES OF THE MOUTH

Infectious Diseases.—Several of the specific infectious diseases are accompanied by characteristic lesions in the mouth. *Herpetic vesicles* upon the lips are especially frequent in pneumonia, malaria, and cerebrospinal fever. Tiny white spots surrounded by a red areola (*Koplik's spots*) are seen upon the inner surfaces of the cheeks and lips before the appearance of the rash of measles. In scarlet fever, enlarged fungiform papillæ of the tongue protrude as scarlet points through the white coating, causing the "*strawberry*" *tongue*. The *smallpox eruption* constantly appears upon the mucous membranes of the cheeks, lips, tongue, and palate, as scarlet spots which soon become painful ulcers. *Chicken-pox vesicles* are often seen upon the palate and soon rupture to form shallow ulcers. In about 7 per cent. of cases of *typhoid fever* small ulcers appear upon the fauces from which *typhoid bacilli* may be cultured. Lesions of *syphilis* occur in the mouth in all stages of the disease. In the lips and tongue the chancre assumes its usual characteristics, a sluggish painless ulcer with infiltrated base, healing with slight deformity. In the secondary stage the mouth is practically always affected. There are injection and soreness of the throat; and usually on the sides of the tongue, buccal surfaces, and inner surfaces of the lips the shallow erosions known as mucous patches appear. These are inflamed, a dirty gray color, level or slightly raised above the surrounding tissues, and their discharge swarms with *Spirocheta pallida*. Condylomata may be seen upon the skin at the angles of the mouth and are also exceedingly infectious. In the later stages gumma develops in the lip and tongue. Gumma of the tongue, if single, is usually found about the middle of the dorsal surface. At first deep within the tissues, it soon approaches the surface and breaks down to form a deep, sharply punched-out ulcer. Late in the disease the tongue is often found to be shrunken, smooth and harder than normal, with atrophy of the papillæ. The smooth atrophy of Virchow may be felt upon the posterior surface. Gumma of the lip is similar to that of the skin, while gumma of the hard palate rapidly causes necrosis of the bone and perforation.

Tuberculosis occurs in the mouth; and is derived primarily from milk or dirty fingers, secondarily from tuberculous sputum, or from extension of *lupus vulgaris* from the face. The lesions are most frequent on the lips, on the tip and edges of the tongue, and on the soft palate. Usually several small yellowish nodules appear at once in various parts of the mouth. These soon ulcerate and gradually enlarge. About the ulcer are usually a few tiny nodules. The discharge is thin and blood-tinged and contains *tubercle bacilli*. Healing is very slow.

Foot-and-mouth disease rarely occurs in man. After an incubation period of about a week, small vesicles develop upon the mucous membranes of the mouth, and an erythematous eruption appears on the hands. The oral vesicles soon rupture, ulcerate, and disappear within a few days.

Several of the *tropical diseases*, rarely seen in the United States, such as leprosy, yaws, gangosa, American leishmaniasis, and verruga peruviana, attack the structures in and about the mouth.

Inorganic substances absorbed in small amounts for variable periods of time may cause lesions in the mouth.

Mercury, from occupational exposure, or from its therapeutic use, causes a condition known as ptyalism or mercurial salivation. There is first a metallic taste with soreness of the teeth upon chewing. Continued absorption results in an increased secretion of the saliva which is described as ropy; swollen, tender, spongy gums which bleed easily; swelling and soreness of the salivary glands, especially those under the tongue; and a foul breath. In extreme cases ulcers appear upon the gums, cheeks, tongue, and palate; the teeth loosen and may fall out, and the jaw may undergo necrosis. When even moderately intoxicated the patient is quite wretched; suffers considerable pain which is made worse by attempting to eat; may lose weight, appear cachectic, and eventually die.

If administration of or exposure to mercury be stopped when soreness of the teeth is first noted no trouble ensues, and the mouth symptoms disappear in a few days without any treatment. In more severe cases the mercury must be eliminated from the body by a saline purge, a hot bath night and morning, and ingestion of plenty of water. Potassium iodid is thought to favor excretion of the drug, and atropin sulphate reduces the excessive secretion of saliva. In the worst cases rectal irrigations with solutions of potassium acetate (1 dram to the pint), as advised by Lambert and Patterson for acute poisoning, are useful and may be life-saving. A potassium chlorate mouth-wash should be prescribed. The patient must be fed; liquids are the least objectionable form of nourishment. Milk, with eggs, cream, and lactose, furnishes a diet of high caloric content which can be taken with little pain. It may be necessary to administer an opiate. When mercury is to be given continuously the patient should be carefully instructed in the care of the mouth. The cleaner it is kept, the more mercury can be given without producing toxic symptoms. The teeth should be cleansed and a mouth-wash used after each meal; and twice daily the patient should put several drops of tincture of myrrh on the tooth-brush before vigorously brushing the teeth and gums.

Bismuth.—Some years ago surgeons were familiar with the lesions caused by absorption of bismuth mixtures used in the dressing of sinuses and other wounds. Lately preparations of bismuth have been widely used for intramuscular injection in the treatment of syphilis, and the toxic effects of overdoses of the metal are again common. Bismuth causes pigmentation of the mucosa of the mouth, stomatitis, renal irritation, colitis, anemia, and erythematous skin eruptions. Warner has examined several of the preparations used for intramuscular injection and has found the bismuth content to vary from 35 to 65 per cent., and that several specimens contained impurities.

Pigmentation of the mucosa is frequently seen (Hopkins, "most patients," Heckelmann, 27 per cent. of hospital patients, 8 per cent. of private patients), but the *bismuth line* is the more common manifestation. It is located at the margin of the gum, is bluish black, and wider and less sharply defined than the lead line. It is presumably a deposit of bismuth sulphid formed by combination of the hydrogen sulphid from bacterial decomposition

with the bismuth. Its presence or extent is probably indicative of the degree of cleanliness of the mouth. Less frequently there is more extensive pigmentation, blackish plaques of variable size on the gums and mucosa, punctate or diffuse pigmentation of the soft palate, blackening of the filiform papillæ of the tongue and even of the veins under the tongue. The pigmentation usually disappears within two or three months after cessation of administration of bismuth.

Stomatitis develops in about one-fifth of the patients who receive injections of bismuth, and, as a rule, its severity varies directly with the extent of pigmentation. Usually there is gingivitis, salivation, and a foul breath which subside when the drug is discontinued. When more severe, ulceration takes place, most often about the third molar teeth, but also along the margin of the gum and in the floor of the mouth. The ulcers become infected, the salivation more marked, the breath horribly foul, and anorexia, and, in the worst cases, cachexia, develops because food causes pain. Several fatalities from stomatitis have been reported.

The administration of bismuth must stop at the first sign of gingivitis. When the intoxication is severe, and insoluble preparations have been injected, it may be wise to cut down upon and evacuate any residue. In mild cases local applications and frequent mouth washing are sufficient. As the infecting organism is often Vincent's spirillum, applications of arsenic have been advised. Acriflavin has been advocated in the more severe conditions, but eliminative treatment and attention to feeding are also necessary.

Careful attention to oral hygiene enables the patient to take more of the drug without the development of mouth lesions.

Potassium iodid or any iodin compound may cause toxic symptoms. Coryza is the most common of these, but some patients complain of a coppery taste, of swelling of the mucous membranes, and of soreness of the salivary glands, with increased secretion of saliva. In rare cases patients become sensitized to minute doses, and marked swelling of the lips, tongue, and larynx results.

Exposure to *lead* or any of its salts causes the appearance of a bluish-black line upon the gums. Upon close inspection the line is seen to be made up of minute dots which are caused by a deposit of lead sulphid in the papillæ at the margin of the gums.

Diseases of the Skin.—Many diseases of the skin are accompanied by lesions of the mucous membranes of the mouth, but only the more frequent will be described.

Dermatitis herpetiformis (*hydroa*) is a chronic disease occurring in attacks of variable severity characterized by the formation of small bullæ and erythematous patches upon the skin and vesicles in the mouth. The severe itching of the skin is the outstanding complaint. The mouth vesicles rupture almost at once, and develop into small bright red ulcers which soon heal.

All forms of *pemphigus* are accompanied by the development of bullæ upon the mucous membranes. Acute forms of the disease terminate fatally in three to four weeks. In the chronic forms bullæ may appear in successive crops in the mouth for months before any skin lesions appear. The mouth bullæ soon rupture and leave painful shallow erosions which are covered with a diphtheroid membrane. The disease may last for months

or years and nothing can be done to influence its course. Ulcers in the mouth are kept clean by the use of mild antiseptic mouth-washes.

In *erythema multiforme* an eruption, usually bullous, may occur upon the mucous membranes. The bullæ soon become shallow erosions covered with a dirty membrane, and may be mistaken for the mucous patches of syphilis. The history of recurring attacks, the accompanying rash upon the skin, and the failure to find *Spirocheta pallida* all serve to differentiate the disease from syphilis. No other treatment than cleanliness of the mouth is necessary.

Lichen planus is, by some investigators, thought to be an infectious granuloma. The skin lesions consist of a series of lilac colored papules with angular outlines which appear most commonly upon the flexor surfaces above the wrist, on the inner sides of the thighs, and on the back of the neck. The eruption on the mucous membranes is usually on the buccal surfaces, is papular, non-inflammatory, feels somewhat rough, and may appear to be connected by a network of fine white lines. On the tongue oval plaques are scattered irregularly; these look like mucosa to which silver nitrate has been applied. The severe afebrile onset of each attack, the distribution and angular outlines of the skin lesions, the intense itching, and the recurrent acute outbreaks all serve to differentiate the lesions from those of syphilis. The treatment is the internal administration of arsenic or mercury; a mouth-wash may be used.

Lupus erythematosus appears upon the mucous membranes of the lips in about 25 per cent. of cases. The disease passes through an inflammatory and atrophic stage. There is first a shallow erosion, the edges of which later become elevated while the center deepens and becomes covered with a dirty yellowish membrane. With healing there is atrophy, and a bluish-white scar forms. The lesions of the mucous membrane usually accompany the erythematous and scaly types of skin lesions, and it is these lesions upon the face which are of the greatest assistance in making the diagnosis. Trichloracetic acid (50 per cent. solution) or resorcin in alcohol have been advised as applications for the mouth lesions.

Papillomata and warts of various kinds form upon the mouth and lips. They should be removed with carbon-dioxid snow or with radium. A *xanthoma* may be seen upon the buccal surfaces or upon the edge of the tongue. This does not require treatment.

Fordyce's disease is often encountered. It is characterized by the formation on the inner surfaces of the cheeks and lips of many small yellow tumors level with the surface of the surrounding mucous membrane. These are non-inflammatory and cause no symptoms. No treatment is required.

Deficiency Diseases.—Several diseases which are probably due to deficiency of an essential part of the food produce characteristic lesions of the mouth. A discussion of the treatment of these is omitted here, as it is included in the sections devoted to these diseases.

Scurvy, when well marked, causes swelling, soreness, and bleeding of the gums; in severe cases there is ulceration and the teeth may fall out. The tongue and salivary glands swell, and there are hemorrhages under the mucous membrane of the palate. Diagnosis is made from the history of the diet and from other signs of the disease.

In *pellagra* the mucous membranes of the mouth are reddened, denuded of epithelium, and may be ulcerated. The tongue is swollen, coated in the

center, but bright red at the tip and edges; the gums also are swollen. The patient complains of a sensation of heat and of loss of the sense of taste. The diagnosis is made from the seasonal incidence of the disease, the accompanying changes in the skin of the face, hands, and neck, and the psychosis.

Sprue causes, as one of its earliest symptoms, soreness of the tongue. Upon examination there are found loss of the epithelium, small vesicles or ulcers, and swelling of the fungiform papillæ. The color is not so deep as that seen in pellagra, nor is the discomfort so marked. Other characteristic evidences are the bulky fatty stool, the anemia, and the small liver.

Diseases of the blood-forming organs and of the spleen cause mouth lesions.

The red, engorged-almost-to-bursting appearance of the mucous membrane of the mouth in *polycythemia* is very characteristic.

Bleeding from the gums is seen in *jaundice* from any cause, but is especially frequent in hypertrophic cirrhosis and in the various forms of hemolytic icterus. It also occurs in the splenomegalic anemia of *Banti's* and *Gaucher's diseases*. In *idiopathic aplastic anemia* or in the secondary types from *benzol poisoning or chronic infection*, petechial spots are seen and bleeding from the gums occurs, while in *purpura hæmorrhagica* bleeding from the mucous membrane of the mouth may be serious.

Pernicious anemia, in its early stages, is often accompanied by soreness with patchy redness of the tongue and buccal mucosa. Pyorrhea alveolaris is also frequent. In the late stages of pernicious anemia the tongue becomes pale and flabby with marked atrophy of the epithelial coating. Areas of slaty looking pigmentation are seen in some cases on the cheeks, lips, and edges of the tongue. Pigmentation of the mucous membrane of the mouth is also seen in disturbances of the function of the *suprarenal glands*, such as Addison's disease and retroperitoneal growths. *Arsenic* may cause similar pigmentation, as will also bismuth.

In *leukemia* of either type there may be bleeding from the gums, or the first sign of the disease may be an intractable hemorrhage from the socket of a recently extracted tooth. Late in the chronic forms or at the onset of the acute forms acute stomatitis frequently develops and progresses to severe ulceration.

SAMUEL BRADBURY.

LOCAL DISEASES OF THE GUMS, TONGUE, LIPS, AND TEETH

Oral Sepsis.—The common source of chronic sepsis in the mouth is infection about the teeth. This may take the form of abscesses about the tooth roots (alveolar abscess) or pyorrhea alveolaris. An *alveolar abscess* usually results from caries of a tooth, destruction of the pulp, and ascending infection through the root canals. The abscess may be acute and soon push through the gum, to form a "gum boil"; or it may be chronic and cause no local symptoms. *Pyorrhea alveolaris* is an infection superimposed upon another condition which is not thoroughly understood. Various conditions, possibly collections of tartar or improper dental fittings, more probably age, chronic illness, and improper diet, cause the tooth to become partially

separated from its socket, so that pockets, which may extend as far as the tip of the root, form between it and the gum. Sepsis follows absorption of toxins and bacteria through the blood-stream; and some observers believe that there is direct infection of the stomach wall, gall-bladder, intestine, and appendix from the swallowed pus.

Pyorrhea and alveolar abscesses are exceedingly common, and often cause no symptoms. Sometimes, however, there is a general subnormal health level, at times associated with a moderate degree of anemia; and relatively seldom serious consequences result, such as chronic infectious arthritis, infection of the heart valves or kidneys, or even of the blood. It often seems that oral sepsis causes symptoms only after the devitalizing effect of an attack of infectious disease or an exhausting period of hard work or worry.

Oral sepsis belongs primarily in the domain of preventive medicine, for in all individuals, either sick or well, it is a potential source of trouble. Evident infection, dentures which cause irritation of the gums, devitalized teeth whether tender or not, and teeth which are loosened or tender in the slightest degree should be examined by a competent dentist. In any disease which experience has shown to be due to focal infection, the teeth should be carefully examined by a competent dentist and with the Roentgen ray.

Stomatitis.—For many years physicians have associated attacks of stomatitis with nutritional or gastro-intestinal disturbances. Recently Gerstenberger has suggested that the primary factor in stomatitis is a deficiency of water-soluble *B* vitamin, and that infection is a secondary development. Recovery is reported in a remarkably short period upon the administration of pure water-soluble *B* vitamin without local measures or change in the diet. The possibility of this nutritional deficiency should be borne in mind, and even in apparently well-nourished patients with stomatitis the administration of water-soluble *B* vitamin is well worth a trial, although local measures are also necessary. Gerstenberger suggests the juice of canned or fresh tomatoes as a readily available source of the necessary vitamin.

Catarrhal Stomatitis.—In infants and children, the common causes of catarrhal stomatitis are digestive disturbances, rough washing of the mouth, or allowing the child to suck unclean articles. For the adult digestive disturbances, traumatism by hot or highly seasoned food, and the excessive use of tobacco are usually responsible. Uncared for and carious teeth are predisposing factors. At all ages catarrhal stomatitis accompanies other forms of stomatitis and also the infectious diseases.

There is acute inflammation with swelling, redness, and tenderness in the gums, cheeks, and lips. The tongue is coated and slightly swollen; there is salivation and the patient complains of soreness and a bad taste in the mouth. General symptoms are not observed in adults, but infants are restless and irritable, refuse to eat, and may have slight fever and diarrhea. The disease lasts from three days to a week in otherwise healthy individuals.

Food should be liquid or semisolid. Mild mouth-washes, such as potassium permanganate (1 : 8000), or a saturated solution of boric acid, or tincture of myrrh (1 : 50 in water), should be used frequently. In infants the same solutions should be gently applied on pledgets of cotton. The apparent causative factor requires attention.

Aphthous Stomatitis (*Herpetic Stomatitis, Canker*).—Aphthous stomatitis is seen in children from two to four years of age, but is not infrequent in adults, particularly in women during menstrual periods or pregnancy. Recurrence is frequent, and in some individuals seems to depend upon nervous or emotional factors. Disturbances of digestion, uncleanliness of the mouth, and even chronically infected tonsils and adenoid vegetations have been held responsible.

Small vesicles occur singly or in groups on the inner surfaces of the lips or cheeks, at the base of the alveolar process, or under the tongue. The vesicle breaks almost immediately, leaving a superficial ulcer 1 to 3 mm. in diameter, covered with a yellowish exudate, and surrounded by a zone of hyperemia.

The condition makes children restless and fretful; they refuse to eat and may have slight fever. Adults have no general symptoms, but complain of discomfort and find that food causes burning pain. There is salivation, slight fetor of the breath, and a coating of the tongue. Treatment should be directed toward any digestive complaint. Mild mouth-washes such as those used for catarrhal stomatitis should be advised. The ulcers themselves may be touched with the silver nitrate stick.

Ulcerative stomatitis is less frequent than catarrhal or aphthous stomatitis and rarely develops in persons who are in good health. It is seen in children over four years of age among the poorer classes or in adult inmates of institutions or jails where it may spread in the manner of an epidemic. There are often local devitalizing factors such as carious teeth and accumulations of tartar. Crowding, bad food, and poor hygiene appear to play a rôle in its etiology. No specific organism has been described, and it may be that the apparent institutional epidemic is due to a diet which is deficient in some respect.

The disease begins at the margin of the gum with swelling, redness, and oozing of blood upon slight manipulation. The original lesion is usually in the lower jaw in front of the incisors or to the outer side of the molars. The inflamed area becomes necrotic, and the ulceration spreads along the free border of the gums to the cheek, and edges and lower side of the tongue. The diseased tissues are covered with a yellowish slough which is firmly adherent. The nearby lymphatic glands are enlarged and tender, there is marked salivation, coating of the tongue with slight swelling, and a putrid odor to the breath. Mastication is exceedingly painful and, in debilitated children, there is fever, fretfulness, and prostration. In the worst cases the ulceration may extend to the alveolar process and cause loss of the teeth and necrosis of the bone. A few cases in children progress to noma. "An exanthem may occur and be mistaken for measles" (Osler).

The general health must be improved. Sufficient food must be given, in children by gavage if necessary, preferably in the form of cool liquids or soft solids. Carious teeth and necrosed bone should be removed.

Potassium chlorate is almost a specific. The dose for an adult is 10 grains three times a day, for a child of six years, 3 grains every four hours. It should be well diluted. Mouth-washes of potassium permanganate (1 : 8000) should be used frequently. The ulcers may be touched with silver nitrate.

Gangrenous Stomatitis (*Noma, Cancrum Oris*).—Gangrenous stomatitis almost always occurs in debilitated children of two to five years of age.

The preceding illness is usually one of the infectious diseases, especially typhoid fever or measles, or a chronic enteritis or other digestive disturbance. No specific organism can be found as the cause, but the fact that there have been apparent epidemics in institutions and the horrible nature of the malady necessitate strict quarantine of every case. The disease is essentially a rapidly spreading gangrene without tendency to limitation.

Often the first manifestation is an extremely offensive odor of the breath. Upon examination there is found upon the buccal surface, gum, or inner side of the lip a small ulcer covered with gray or black slough, and surrounded by inflamed edematous tissue. This spreads rapidly both laterally and in depth. In a remarkably short time the skin over the cheek becomes brawny, then red and tense, finally black and broken. Gangrene rapidly destroys a large portion of one side of the face and attacks the tongue, palate, and gums, causing the teeth to fall out. Pain and fever are not marked, but the child is soon prostrated. The usual interval between onset and death is five or ten days. The few children who recover are markedly deformed. Bronchopneumonia, abscess of the lung, and severe diarrhea are frequently associated with this condition. A fatal adult case of gangrene of the lips, alæ of the nose, and vulva has recently been reported by B. M. Phillips as "spirochetal gangrene (noma)." The micro-organisms in the discharge from the lesion were nearly all fusiform bacilli and spirochetes.

Treatment consists in early and thorough excision of the gangrenous area followed by application of the cautery or nitric acid. No consideration can be given to the cosmetic effect. If the child recovers, plastic repair of the face may follow. Diphtheria bacilli have been cultured from the gangrenous area in some cases, and whenever they are present large doses of diphtheria antitoxin should be administered.

Ulceromembranous stomatitis is the name given to infection of the gums by the fusiform bacillus and spirochete described by Vincent. It may occur alone, as in the "trench mouth" of soldiers, or may accompany an infection of the tonsil.

The accompanying symptoms and appearance of the lesion are similar to those of ulcerative stomatitis, although isolated patches of the disease upon the buccal surfaces, tongue, and palate are more common. The infection is obstinate, difficult to eradicate, and recurs frequently. The diagnosis is easily made from smears from the infected gums. The presence of diphtheria bacilli can be excluded because of their rarity in the mouth and by culture.

The disease may be prevented by scrupulous attention to oral hygiene. Carious teeth and chronically infected tonsils harbor the organism.

Mild cases will recover upon the use of topical applications, such as tincture of iodin, 10 per cent. silver nitrate solution, and potassium permanganate used either in 1 per cent. solution as an application or diluted 1 : 2000 as a mouth-wash.

In severe or obstinate cases arsenic gives better results. The best local applications are Bowman's solution, a mixture of glycerin (8 c.c.), wine of ipecac (12 c.c.) and *liquor potassii arsenitis* (12 c.c.) or arsphenamin (0.3 gm. in glycerin 10 c.c.). Four to 6 drops of Bowman's solution should be used on a soft tooth-brush three times daily with vigorous brushing. The arsphenamin solution, on small pledgets of cotton, may be inserted into the ulcers for twenty minutes three times a day. Fowler's solution has been

used for local application, but may be dangerous if the lesion is extensive. A mouth-wash of sodium perborate (2 per cent.) used every half-hour is efficacious.

The intravenous injection of arsphenamin and neo-arsphenamin and the intramuscular injection of sulpharsphenamin are also effective. The preparation of the solutions is the same as for that given in syphilis, but smaller doses are administered—0.3 gm. of arsphenamin or sulpharsphenamin and 0.45 gm. of neo-arsphenamin. Ordinarily one dose is sufficient, but the injection may be repeated at the usual intervals. In protracted cases good food and hematinics are necessary.

Parasitic Stomatitis (*Thrush*).—Parasitic stomatitis is due to a fungus of the class of hyphomycetes known as *Oïdium albicans*. It infects the mouths of debilitated infants or those whose mucous membranes have been injured by violent cleansing, by neglect, or by mild stomatitis. It is seen occasionally in adults after a severe infection or in the late stages of chronic illnesses.

The infant first refuses to nurse or has difficulty in swallowing. There may be diarrhea with much irritation of the buttocks. The mouth appears dry, and scattered over tongue, gums, cheeks, and lips are small white patches which look somewhat like milk curds. These patches are of irregular shape, slightly raised, and can be removed only with difficulty. After removal there is an hyperemic area which may bleed slightly. The diagnosis is readily made by examination of a fresh crushed specimen. The usual attack lasts but two or three days. In unusual instances the infection may extend to the esophagus and pharynx, and rarely to the trachea, lungs, and skin of the fingers and face. A case of systemic infection has been reported.

The mouth should be gently and frequently cleansed with cotton wet with a saturated solution of boric acid or a mild alkaline mouth-wash. Any digestive disturbance requires attention.

The disease can be prevented by oral hygiene and cleansing of the baby's bottles and nipples, and the maternal nipple.

Mercurial and **bismuth stomatitis** have been commented upon (see p. 605).

Ludwig's angina is an acute streptococcic infection of the floor of the mouth. The disease begins suddenly with marked constitutional symptoms and swelling under the jaw which rapidly extends into the neck. The floor of the mouth becomes swollen and indurated, and the tongue pushed upward.

Treatment should begin early. It consists of free incision and drainage of the infected tissues. The disease is frequently fatal.

Bednar's aphthæ are small ulcers upon the posterior part of the hard palate which are caused by unnecessary roughness in cleansing the infant's mouth or from pressure of too long a nipple.

Riga's disease develops in infants after the eruption of the lower incisors. It is especially common in Italy. At first there is an indurated grayish area somewhat elevated above the surrounding mucous membrane on the frenum of the tongue. It may ulcerate later. The affection may last for months, but finally disappears. Treatment is unsatisfactory. The indurated area may be excised or tincture of iodin may be applied periodically.

Other Types of Stomatitis.—The frenum of the tongue may be ulcerated from pressure upon the lower incisors during attacks of whooping-cough.

Stomatitis due to infection by the *diphtheria bacillus* and the *gonococcus* is rare. The diphtheritic type appears in neglected cases of faucial diphtheria. Gonorrheal stomatitis develops in the newborn after infection from the mother. There are yellow or white patches on the tongue or hard palate, but no general symptoms. The gonococcus is found in smears. Recovery takes place in seven to ten days. The treatment consists in frequent cleansing and the application twice daily of 1 per cent. silver nitrate or protargol solution.

Lips.—Harelip is a congenital deformity caused by failure of the frontonasal plate to unite with the lateral process on one or both sides. In the more severe grades the palate is commonly cleft. If the child nurses properly, operation may be postponed to the third month, but if there is difficulty it is advisable to operate at once while the infant is in relatively good condition.

Macrocheilia may be caused by hypertrophy of the mucous glands of the lower lip, but is usually due to lymphangioma which may involve either lip, but more frequently the upper. In lymphangioma there is gradual painless enlargement, sometimes with attacks of acute inflammation. Radium and the *x*-ray have been successfully used in treatment. When there are large lymphatic spaces, surgical ablation of the affected lip is, however, more satisfactory.

Eczema of the lips occurs in adults and in children, especially in those with tuberculous lymph-glands. There are recurrent attacks of inflammation of a narrow band of skin below the lips and the formation of painful fissures. The red border of the lips may be inflamed by exposure to wind, sun, or cold. The fissures are most apt to form in cold weather.

Children must be taught not to lick the lips. In older persons, application of zinc oxid ointment, calamine lotion, or Lassar's paste may be advised. The causative factor should be removed if possible. The edges of fissures should be held together by narrow strips of adhesive plaster.

Herpes Simplex (*Fever Blister*).—Herpes simplex of the lip is especially associated with pneumonia, malaria, and cerebrospinal fever. It may develop repeatedly in certain individuals after minor infections or digestive or emotional disturbances.

Usually only one or two vesicles form on the edge of the lip or inside the mouth. These soon rupture and form small ulcers. Healing takes place in five or six days. The vesicles sometimes may be aborted by painting the area with collodion or by the application of spirit of camphor. After ulceration has occurred zinc oxid, calamine lotion, or silver nitrate solution should be used.

Perlèche is probably a mild infectious disease which attacks undernourished children whose mouths are dirty. Small white opaque patches or blisters form at both angles of the mouth. They are painful and the patient constantly licks them. The affection lasts four to six weeks and is prone to recur. In some respects these lesions resemble those of syphilis, and differentiation must, therefore, be made with care. Perlèche is never seen inside the mouth and there is no induration. The nutrition of patients should be improved and the mouth kept scrupulously clean. The lesions themselves should be touched with 10 per cent. silver nitrate solution. Precautions must be taken to prevent spread of the disease.

Carbuncle of the upper lip may cause septic phlebitis of the facial

vein with progressive involvement of the ophthalmic vein and cavernous sinus. A small pustule with a wide zone of infiltration rapidly enlarges and breaks down. There is fever and prostration. Because of the danger of spreading this condition through the lymphatics, incision or excision are contraindicated. No attempt should be made to open such carbuncles until they have softened. In their early stages wet applications of boric acid are indicated.

Tongue.—Bifid tongue is a rare anomaly which is usually associated with other physical and mental abnormalities. Defective development of the anterior portion of the tongue produces the condition known as tongue-tie. The frenum should not be divided without careful consideration, as many of these tongues become normally mobile later.

Macroglossia is due to congenital lymphangioma which may be apparent at birth or appear after a few years. The remarkable enlargement is caused by gradual growth of the lymphangioma and by repeated attacks of acute glossitis which are probably similar to the recurrent fever of elephantiasis. The tongue may protrude constantly, the external part being dry and fissured. Much difficulty is experienced in talking and swallowing. The external portion of the tongue should be excised and the remaining portion treated by radiotherapy. Enlargement of lesser degree may be treated by radiotherapy alone.

Scrotal tongue is a congenital anomaly. When the sulci between the plications become inflamed and painful, silver nitrate solution should be applied to the fissures.

Enlargement of the lingual tonsil may occur alone or in conjunction with hypertrophy of the lymphatic tissue of the tonsillar ring. The commonest symptom is a persistent, irritating, non-productive cough which is more marked when the patient reclines.

Geographical tongue is seen in children and in adults. One or more small white or yellowish elevations appear, gradually enlarge and desquamate in the center, leaving red patches with broad white circular outlines. These run into one another and make figures with scalloped outlines. The only symptom is a sensation of burning or itching which is aggravated by food. The disease is obstinate, lasting for months or years, and in children especially is often associated with digestive difficulty. Treatment is unsatisfactory, but applications of silver nitrate have been advised.

Black tongue is a rare affection which usually attacks middle-aged individuals. The patient notices a black or brownish patch on the middle of the dorsum of the tongue, but seldom complains of discomfort. Upon examination the discolored area appears to be covered with coarse hairs which are hypertrophied filiform papillæ. The color is not produced by food. Treatment is unsatisfactory, but the patient should be carefully instructed about oral hygiene and given a simple mouth-wash.

Acute glossitis may follow burns, bites, or other injuries, or may develop during an infectious disease such as smallpox or typhoid fever. It is usually characterized by high fever, salivation, marked pain which is referred to the ears, and considerable swelling of the tongue. The neighboring lymph-glands are enlarged. The tongue should be incised and cold applications used. Occasionally the lesion becomes gangrenous. Sometimes abscesses form in the tongue, usually toward the base. These should be incised and drained.

Moeller's glossitis is a superficial inflammation in which irregularly shaped, very red patches appear on the tip or sides of the tongue. There is burning or pain and sensitiveness to hot or spicy foods. The condition is obstinate. Silver nitrate applications, non-irritating food, and mild mouth-washes are advised.

Leukoplakia buccalis is described by Cumston as an epidermization of the mucosa with exaggeration of the characteristics of the epidermis. The disease produces two fundamental lesions—hyperkeratinization of the mucosa and sclerosis of the derma.

The clinical manifestations are of several types: on the tongue small white raised or papillomatous patches or diffuse areas appear which, according to their thickness, are pearly white or slightly cream colored; pearly white plaques form at the angles of the mouth; and, rarely, a diffuse white layer may be seen covering buccal surfaces, gums, inner surfaces of the lips and palate, and sometimes the tongue as well. Most of the lesions begin as thin pearly looking patches which gradually thicken until they are creamy white. The disease occurs less often in women than in men, the relative incidence being 1 to 30. Excessive smoking is one factor in its etiology. While the lesions are not syphilitic and do not respond to antiluetic treatment, the disease is very commonly seen in patients with a history of syphilis. Other irritants, such as carious teeth, alcohol, irritating food, and condiments, may be the cause. The disease is more likely to develop in individuals suffering from anemia, diabetes, and chronic gastro-intestinal disorders.

There are rarely any symptoms except in the older cases, when the tongue may feel somewhat stiff and leathery. The quantity of saliva is usually increased. The lesions may disappear spontaneously, but, as a rule, the patches slowly enlarge, desquamate from time to time, and reform immediately.

As carcinoma is more likely to develop in these abnormal tissues than usual, its prevention is the object of treatment. Freshly formed patches may be treated medically. Tobacco, alcohol, and irritating condiments should be forbidden. Locally, balsam of Peru, silver nitrate, 1 per cent. chromic acid, or 5 per cent. lactic acid may be applied. Hazen says that neither antiluetic treatment nor the Roentgen ray are of any use in leukoplakia.

Old patches or those in which there is any tendency for new growths to form, or which ulcerate or cause pain, should be removed. When these are small, only the plaque need be excised, but with much involvement Cumston advises decortication of the upper surface of the tongue from the circumvallate papillæ forward. The two edges of mucous membrane should be sutured together over the dorsum. He says this rolls the tongue, but that it flattens within a few days.

Tumors and cysts of the structures about the mouth may be of any variety and either benign or malignant. Epulis, ranula, and epithelioma are most frequent.

Epulis is a fibrous tumor of the gum. It is soft, usually pedunculated, and may be lobulated. Frequently it grows opposite the roots of carious teeth. The mucous covering is easily injured and ulceration results. Treatment is excision.

Ranula is any obstructive cyst of the mucous or salivary glands under

the tongue. When the obstruction is sudden or occurs intermittently pain and tenderness result. The cyst may originate in the sublingual salivary gland or its ducts or in the mucous glands about the frenum of the tongue. The treatment is surgical, incision or excision.

Epithelioma is the usual malignant tumor which is seen for the most part on the tip or borders of the tongue and on the lower lip.

Chronic irritation bears the same etiological relation to cancer of the tongue or lip as it does to cancer elsewhere and is furnished by pipe smoking, betel-nut chewing, rough teeth or dental appliances, leukoplakia buccalis, or fissures. Cancer is also likely to develop in scars.

Men are far more frequently affected than women. The usual age for the development of this lesion is that of carcinoma in general, about forty-five to sixty years. The tumor first appears as a small papilloma with infiltration at the base, or, if it begin in a fissure, the earliest signs may be failure to heal and marked thickening of the part affected. Later the tumor ulcerates and gradually enlarges. The base of the ulcer is irregular and covered with a gray necrotic slough. The edges are raised over the surrounding tissue and are distinctly thickened and hard. There is fetor of the breath and, sooner or later, enlargement of the nearby lymph-nodes.

The nature of an infiltrated tumor or an indolent ulcer or fissure in the mouth of an individual who has reached or passed middle age must be immediately determined. The age and sex of the patient are important factors in diagnosis. The possibility of syphilis must be considered and judged by the effect of antiluetic medication. Simple fissures heal readily when properly treated. The safest procedure is biopsy diagnosis. Treatment for carcinoma in either the lip or tongue is wide excision, including all the nearby lymph-glands. The operation should be followed by radiotherapy. Inoperable cases may be treated by *x*-ray or radium, but this does not give satisfactory results.

Samuel Bradbury.

Diseases of the Salivary Glands

The secretion of the salivary glands may be increased or diminished. The normal twenty-four-hour amount in the adult is between 1 and 1.5 liters, the curve of output rising sharply during meals. An apparent increase occurs when swallowing causes pain or when the lips or throat are paralyzed.

Salivation (*Sialosis, Sialorrhea*).—A true increase is known as salivation and may amount to a daily output of as much as 10 liters, although the average amount is between 3 and 4 liters.

The causes of salivation in the order of frequency are:

1. Drugs or poisons, such as mercury, iodin, tobacco, bromids, arsenic, potassium chlorate, jaborandi (pilocarpin), copper, and bismuth.

2. Local inflammation from any form of stomatitis except thrush, from pyorrhea and alveolar abscesses, and from such diseases as scurvy, sprue, purpura, and the anemias.

3. Local irritation from jagged teeth, badly fitting dental appliances, teething, ranula, epulis, and salivary calculus.

4. Infectious diseases, especially smallpox and rabies.

5. Reflex stimulation from the stomach, pancreas, liver, and uterus. Salivation is especially frequent in diseases of the stomach and early in pregnancy.

6. Diseases of the nervous system, such as seasickness and car-sickness, hysteria and migraine, and the more serious organic diseases, such as irritation of the *chorda tympani* usually with paralysis of the seventh cranial nerve, degenerative lesions of the basal ganglia as in *paralysis agitans* and *encephalitis lethargica*, irritation of the vegetative system, *tic douloureux*, and tabes with salivary crises.

7. Idiopathic cases in which no cause can be found. Most cases develop after shock or severe emotion; there is an acute onset, variable duration, and sudden cessation.

Symptoms vary, but when large amounts of saliva are swallowed indigestion and vomiting ensue. In many cases the speech becomes thickened and the taste disordered.

Treatment is that of the cause. Atropin controls excessive salivation and bromids allay nervous symptoms. Exposure of the salivary glands to *x*-ray has been effective in reducing secretion.

Xerostomia (*Aptyalism, Oligosialia*).—Deficient salivary secretion is much less frequent than salivation and is known as xerostomia. The severity varies. The diminution of secretion may be apparent only when eating or may be so marked that mouth and tongue are completely dry.

Mild grades of xerostomia accompany dehydrating diseases, such as *diabetes mellitus, diabetes insipidus,* chronic interstitial nephritis, and cholera. In thrush also the mouth appears dry. Fevers and the drugs opium and belladonna cause dryness of the mouth. The severe types of xerostomia are due to obscure causes and are usually seen in women of nervous temperament who are otherwise in good general health. Some are associated with chronic infection of all the salivary glands, but whether the infection is primary or follows arrest of secretion is unknown. In some cases there is also dryness of the conjunctivæ.

There may be no noticeable abnormality, or the salivary glands may be swollen, and a mixture of thick mucus and pus may be expressed from the ducts. In the severe cases the tongue, lips, and buccal surfaces become dry, shiny, red, and sometimes fissured. The conjunctival sacs may be injected and contain a thick ropy secretion.

Treatment is very unsatisfactory. A glycerin mouth-wash is useful. Small doses of pilocarpin may stimulate the salivary glands. The teeth require careful supervision because early decay is usual and pyorrhea frequent.

Inflammation of the salivary glands may be acute or chronic. In any type except that following calculus the parotid gland is most often involved.

Acute Inflammation.—The commonest acute inflammatory disease is mumps, which is fully discussed in the chapter on Infectious Diseases. Acute inflammation (parotid bubo) occurs as a complication in several diseases, which are usually serious. These are of three distinctive groups: first, acute general infections, such as typhoid and typhus fever and pneumonia; second, injury or disease of the abdominal or genitourinary organs, or after operation upon these structures; and third, diseases

which interfere with the secretion of the salivary glands, such as obstruction of the ducts, facial paralysis, or conditions which cause dry mouth.

As a rule a single gland, usually one of the parotids, is inflamed. The onset is sudden, with an increase of the fever and toxic symptoms already present. The gland swells, becomes tense and tender; there is pain, which is referred to the ear, and interference with swallowing. The swelling rapidly increases, the overlying skin soon becomes red and shiny, and in a few days fluctuation is present.

It is thought that these infections arise from extension through the gland ducts. This seems reasonable when the process occurs during one of the infectious fevers, but it is difficult to understand why parotid abscesses complicate abdominal operations or follow injuries, occasionally quite minor injuries, of the genital organs, and why this complication makes the prognosis so much more serious. Fifty to 60 per cent. of these patients die.

Treatment.—With the onset of the swelling an ice-bag or a poultice may be applied over the affected gland to prevent suppuration in so far as possible. Upon the first indication of the formation of pus the gland must be incised and drained, with care to avoid the large blood-vessels which traverse the parotid vertically, and the facial nerve and its branches, which run through it from behind forward.

In any severe general infection or illness the mouth requires careful attention. Constant cleanliness helps to prevent the development of *parotid bubo.*

Syphilis may cause acute or gummatous inflammation. Sixty-five cases have been reported, 22 occurring in the early stages, 37 in the late stages, and 6 in congenital syphilis. The parotid was involved alone in 53 cases and in 5 cases with other salivary glands. There is gradually increasing swelling and salivation, but not much pain or tendency to suppuration. Both the early and late forms respond to the usual antiluetic medication.

Chronic inflammation is more frequently multiple than acute and may affect all the salivary glands. The usual causes are mumps, syphilis, inflammation of the throat, prolonged exposure to mercury, iodin or lead, and chronic nephritis. Salivary calculi, especially those lodged in the ducts, may cause chronic infection. As a rule, the parotid glands of glass blowers who have gaseous tumors are infected. Of two women that came under personal observation, one had extensive syphilitic scarring of the fauces and hard palate, and the other, marked xerostomia. In each, all the salivary glands were affected and a mixture of thick mucus and pus could be expressed from the ducts. There is impaired secretion and usually slight swelling which varies in degree from time to time.

Treatment is unsatisfactory. The possibility of calculi should be ruled out by careful examination and by *x*-ray. Otherwise the treatment is that of the assigned cause.

Salivary calculi (*Sialolithiasis*) develop in men about twice as frequently as in women. Bacterial infection, stricture from wound or inflammation and possibly foreign bodies are the usual preceding conditions. In two-thirds of the cases the calculus forms in the submaxillary gland or its duct. The stones are composed mainly of phosphates with smaller amounts of organic matter, carbonates, calcium, and magnesia. They vary in size from a diameter of 3 to 30 mm. The largest are found in the glands and

are usually round or irregularly lobulated; duct stones are of small diameter and oval.

A calculus in the gland causes no *symptoms* unless it sets up inflammation, but the patient may notice an unusual swelling before this occurs. Duct calculi first produce symptoms when they cause obstruction. There is sudden pain, often of colicky nature, which is usually felt in the floor of the mouth. It frequently begins with eating when the output of saliva is increased. The duct being blocked, saliva rapidly backs up into the gland and causes marked swelling and pain. The whole condition may be suddenly relieved by a gush of saliva. The swollen gland is readily felt and is quite tender. Often the stone may be found in the duct by palpation. An *x*-ray picture taken to avoid the mandible, readily demonstrates the calculus.

The *treatment* is excision.

Mikulicz's disease is a symmetrical enlargement of, first, the lacrimal, then the salivary, glands. It was described by Mikulicz in 1888. Since then cases have been seen in which there is splenomegaly and local or general lymphadenosis, some with normal blood, others with changes in the blood which are typical of chronic lymphatic leukemia. One male patient seen recently had a typical Mikulicz syndrome and general lymphadenosis. Biopsy on one of the cervical glands showed lymphosarcoma. A very few cases have been seen to change gradually from simple to more severe types; in others, there has been subsidence of the swelling after an acute infection. The usual histology of excised tissue is that of a lymphoma. These facts seem to indicate that this disease ultimately becomes chronic lymphatic leukemia. On the other hand, after complete extirpation of the glandular masses there is no tendency to recurrence nor to involvement of the lymphatic structures.

The swelling progresses very gradually, involving first the lacrimal glands, then the parotids, submaxillaries, and the sublinguals. In some cases, accessory glands on the hard palate and on the tip and edges of the tongue share in the enlargement. The picture is not always complete; the lacrimal glands may be involved alone, or they or any one or more of the salivary glands may escape. The glandular masses are firm, smooth, painless, not tender, and not adherent to the surrounding structures.

The patients complain of their appearance and of difficulty in vision caused by ptosis of the eyelids and interference with the movement of the eyeballs. Excretion of saliva is usually so deficient as to cause difficulty in mastication and deglutition, and the diminution of the excretion of the lacrimal glands causes irritation of the conjunctiva. As a rule the patient remains in good general health.

A few cases are due to syphilis or tuberculosis, but most can be ascribed to no definite cause. Men are more frequently affected than women, and while the disease occurs in children, the usual age of onset is between twenty and forty years.

Treatment.—The internal administration of arsenic and potassium iodid has proved a satisfactory form of treatment in most cases. Exposure to the Roentgen ray has been successful in a number of patients. Surgical removal of affected glands is satisfactory in selected cases.

Tumors.—Almost any type of tumor, either benign or malignant, may develop in the salivary glands, but 95 per cent. are of the mixed variety.

In 75 per cent. of the cases the parotid is involved. The origin of such mixed tumors has occasioned wide discussion and is not yet determined. Ewing inclines to the view that they all arise from epithelial cells—usually misplaced fetal remnants.

The tumor is first noticed as a small nodule in the gland tissue which may remain quiescent for years; then enlargement begins, either slowly or rapidly. The tumor may feel very dense or quite soft according to the type of the predominant tissue; it is rarely tender, usually smooth, but sometimes lobulated or even composed of several distinct tumors. Most of them are encapsulated.

The best *treatment* is early and complete excision followed by exposure of the area to the Roentgen ray. Local recurrence is frequent. The recurrent growths are usually more malignant. Metastasis is unusual.

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DISEASES OF THE PHARYNX

Acute Pharyngitis (*Sore Throat, Angina Simplex*).—INCIDENCE.—Acute inflammation of the mucous membrane of the pharynx occurs in individuals whose general condition is poor or whose habits of life are faulty. The incidence is higher in spring, fall, and winter than in summer.

This disorder is frequently the initial or early symptom of some acute infectious disease, such as acute coryza, scarlet fever, measles, or influenza. Early secondary syphilis of the pharynx often resembles acute pharyngitis.

ETIOLOGY.—Exposure to drafts and chilling of the body after violent exercise are frequent causes.

SYMPTOMS.—The disease may start with a slight chill or more frequently with a sensation of chilliness. This is followed by dryness in the throat and irritation in the nasopharynx. Soon the throat becomes painful and swallowing difficult. Examination of the throat at this time reveals a mucous membrane which is red, swollen, and covered with whitish mucus. The general constitutional symptoms of a mild febrile condition are present. In very mild cases the temperature may not rise at all. Acute pharyngitis lasts from one day to two weeks, and is usually self-limited. Not infrequently, however, the infection extends upward into the nasal cavities or downward into the larynx and trachea.

DIAGNOSIS.—The fact that for some time (twenty-four to seventy-two hours) it may be the only local symptom of an acute infectious disease must be especially borne in mind when marked congestion of the throat is associated with severe general symptoms. The condition in itself is not difficult to recognize.

TREATMENT.—Therapeutic measures should be of such a character as not only to hasten recovery, but also to prevent recurrence of the disease.

The general physical condition of the patient must be determined, the habits regulated suitably, and any predisposing factors, such as deviation of the septum and infection of the sinuses or tonsils, be eliminated. At the onset of an attack a laxative (preferably castor oil) should be administered, and the patient put to bed. Patients with fever ought to remain in bed until the temperature falls to normal; those in whom the disease is afebrile may get up after the first twenty-four hours.

For local treatment there is nothing more satisfactory than irrigation of the throat with a solution of sodium bicarbonate (1 teaspoonful of soda in 1 quart of water), either hot or cold. This may be supplemented by the application of an ice collar or cold compresses to the throat. Local antiseptics are not beneficial in the acute stage and should be avoided. A soft, simple diet is desirable.

Chronic pharyngitis (*chronic sore throat*) is usually a disease of adults. It frequently develops in individuals compelled to work in dusty, unhygienic surroundings, and in those who use the voice improperly and to excess. Habitual alcoholics and smokers are also disposed to the disease. The condition is often associated with general systemic abnormalities such as gout, rheumatism, and certain chronic diseases of the circulatory and respiratory systems.

Types of the Disease.—Chronic pharyngitis is of three types—the hypertrophic, the atrophic, and the chronic granular type. The *hypertrophic type* is characterized by general thickening and congestion of the mucous membrane of the pharynx which is thereby rendered velvety in appearance. The *atrophic type* is probably a late stage of the hypertrophic and is evidenced by abnormal thinness of the mucous membrane which is whitish, glistening, and at times wrinkled. In the *chronic granular form* (clergyman's sore throat) the hypertrophic changes are particularly marked in the lymph-follicles of the posterior pharyngeal wall, and on the lateral walls behind the posterior pillars of the palate.

Symptoms.—The symptoms are a constant sense of irritation or fulness in the throat, the dropping of mucus from the nasopharynx or its collection in the throat, and, at times, difficulty in swallowing. Some patients cough and develop the habit of clearing the throat.

Complications.—The chronic inflammation not infrequently invades the eustachian tube and middle ear, so that deafness ensues. Subjects of the disease are suceptible to laryngitis and inflammation of the trachea and bronchi.

Diagnosis.—Examination of the throat and nasopharynx with either direct or reflected light permits easy diagnosis of chronic pharyngitis. In the granular type the rounded masses of lymphatic tissue are visible in the postpharyngeal wall and behind the posterior fauces of the palate. In the atrophic form the mucous membrane is seen to be pale and glistening and at times covered with brownish crusts. Coakley says that the cicatricial tissue left by an old syphilitic, tubercular, or lupoid ulcer may at times be mistaken for atrophic pharyngitis, but that this tissue has a white puckered appearance different from that of the mucous membrane of atrophic pharyngitis.

Prognosis.—The symptoms of chronic pharyngitis, while annoying, are not incompatible with fair general health.

Treatment.—The treatment of this condition is both local and general.

The *general measures* consist in making the general health as good as possible. Alcohol and tobacco should be forbidden, and the patient taught to use the voice properly, and not to excess. Infected tonsils ought to be removed and any abnormal condition in the nose corrected, surgically if necessary. Aside from irrigation of the nose and throat with alkaline solutions to remove tenacious crusts and mucus, *local treatment* is best performed by the specialist. The results are apt to be discouraging. The success of treatment depends on the duration of the disease and on the possibility of relieving the underlying predisposing cause.

Retropharyngeal Abscess.—A retropharyngeal abscess is an accumulation of pus in the submucous connective tissue of the pharynx.

Etiology.—This occurs most frequently in infants and children between six months and four years of age, but has occasionally been seen in adults. The incidence is high in the apparently healthy infants of the poor. Coakley states that tuberculosis, rickets, and inherited syphilis are predisposing factors. Occasionally the disease is secondary to tuberculosis of the cervical vertebra.

Morbid Anatomy.—The abscess is usually due to streptococcus infection of the retropharyngeal lymph-nodes in the submucous connective tissue of the pharynx. These glands enlarge and later break down and form an abscess. The pus may burrow beneath the mucous membrane, so that at times a large abscess develops which seriously interferes with laryngeal function.

Symptoms.—The onset of a retropharyngeal abscess is manifested by fever, irritability, and crying. These symptoms are soon followed by difficulty in swallowing and refusal of the infant to nurse or take the bottle. The cry at times is of a peculiar, quacking character, described by Regnier as "le cri de canard." Dyspnea may occur and with the cough produce a syndrome resembling that of croup. The temperature may be high, and on account of the inability to swallow emaciation is at times rapid and extreme. If untreated, the abscess may rupture spontaneously during sleep and cause death by suffocation, or produce suffocation and fatal inanition without rupture. When the lesion is not severe there may be no apparent symptoms except those of nasal obstruction which are often discovered only during the routine digital examination for adenoids.

Diagnosis.—The diagnosis of retropharyngeal abscess is usually easily made by inspection or palpation. If the mouth is opened with a tongue depressor, a smooth oval swelling is visible on the posterior wall which pushes forward the palate and uvula. By digital examination this is found to be smooth and elastic, and fluctuation is often easily obtained. Symptoms of *croup* must be carefully distinguished from those of a retropharyngeal abscess.

Prognosis.—If the abscess is evacuated early, recovery is usually good, but if the patient is first seen in the later stages of the disease when dyspnea and prostration are marked, death may ensue, even after prompt draining of the lesion. Tubercular abscesses and those which follow vertebral caries are apt to end less favorably.

Treatment.—The only treatment is early incision to permit free drainage. Most abscesses can be opened suitably through the mouth, when the child is held by the nurse with the head lower than the body and the mouth wide open. The incision should be made through the

mucous membrane in the median line, beginning opposite the larynx and passing upward toward the palate. It is necessary to guard the blade of the scapula with the finger or a piece of adhesive tape about $\frac{1}{4}$ inch from the point. Care should be taken to avoid injury to the soft palate. When the pus ceases to flow from the mouth and nose, the abscess should be gently pressed with the finger to remove any purulent material which may remain. Since the cavity sometimes refills and must be redrained, it is desirable to watch the child closely for a few days after this operation. If dyspnea and weakness place the patient in danger, speed is necessary, but under ordinary conditions there is no need of performing the operation very rapidly. If a retropharyngeal abscess is suspected to be tubercular in origin, secondary infection is best avoided by external incision along the anterior border of the sternomastoid. This procedure should not be performed by the general practitioner. After evacuation of the abscess, measures should be employed to restore the child to its normal condition. Life in the open air, and the administration of tonics, such as cod-liver oil and iron, are desirable. Usually the relief after evacuation is immediate.

Angina Ludovici (*Ludwig's Angina, Cellulitis of the Neck*).—Johnson has described angina ludovici as a more or less violent, purulent, and sometimes gangrenous inflammation of the tissues occupying the submaxillary region of the neck. The characteristic symptoms are those of severe sepsis; the formation of a hard, tense, brawny swelling in the submaxillary region; great pain; difficulty in speaking and swallowing; and sometimes cyanosis and dyspnea caused by pressure on the larynx or by swelling and edema of the throat. If unrelieved by early incision, the whole side of the neck becomes red and hard, the constitutional symptoms threatening, and the local symptoms of interference with respiration alarming. This condition is usually secondary to violent infection of the throat or tonsil usually by a streptococcus, occasionally by a staphylococcus. When severe, the prognosis is grave and the practitioner should early seek the advice of a competent surgeon.

Neuroses of the pharynx are motor and sensory. The most common *motor neurosis*, that known as *globus hystericus*, is a spasm of the motor nerves which causes the sensation of a lump in the throat and is usually associated with enlargement of the lingual tonsil or lingual varicosity. *Spasmodic contraction of the pharynx and esophagus*, which causes swallowing of air with subsequent eructation, is occasionally seen in chorea. The *treatment* of these conditions is mental, with correction of the causative factor.

Sensory Neurosis.—Anesthesia of the pharyngeal mucosa occasionally complicates general nervous disorders. It is most common in hysterical patients.

Hyperesthesia frequently accompanies chronic inflammation of the pharynx.

Paresthesia (sensations of suffocation, tickling, itching, or of the presence of foreign bodies) is not uncommon in the neurotic or insane.

T. Laurence Saunders.

Diseases of the Tonsils

Peritonsillitis (*Quinsy, Quinsy Sore Throat*).—Definition.—Peritonsillitis is a collection of pus in the connective tissues adjacent to the tonsil.

Etiology.—It is usually if not always secondary to acute or chronic tonsillitis. Although comparatively few cases of tonsillitis are followed by quinsy, when this condition has once occurred the individual is always liable to a recurrence after tonsillitis. The condition is usually seen in young adults; children are not immune, however, and occasionally it is seen in elderly patients. The organisms found are usually those infecting the tonsil.

Morbid Anatomy.—Usually a collection of pus is found in the connective tissue of the soft palate above the tonsil. More rarely the site of the abscess is between the tonsil and the posterior pillar or below the tonsil in the lateral pharyngeal wall. The latter type of abscess is more serious because extension of the inflammation may cause edema of the larynx. Typically marked swelling can be observed in the soft palate above the tonsil; this does not extend to the opposite side because of the fibrous median raphé of the palate. The uvula, which is red and edematous, lies against the tonsil of the affected side. The swelling is tender and painful to the touch. When the abscess is marked, fluctuation can be elicited by the palpating finger. The lesion is usually unilateral, but may at times be bilateral. The tonsil is red, swollen, and may project beyond the median line; its crypts are full of exudate; and the anterior pillar is prominent. The quantity of pus varies from a few drops to several drams. Occasionally the lesion seems to consist of exudation and inflammation adjacent to the tonsil, in which pus is apparently absent. If untreated these abscesses usually rupture spontaneously into the pharynx, and are thus at least temporarily cured. Death, however, is known to result from edema of the larynx, sepsis, and general exhaustion.

Symptoms.—In general the symptoms are those of acute tonsillitis with profound general symptoms. The temperature is higher, the prostration more extreme, and the patient more septic. The local changes may disappear on one side, while on the other the soreness becomes more intense and swallowing more difficult. The pain assumes a radiating character, shooting up to the ear on the affected side. Tenacious mucus in the pharynx annoys the patient and resists efforts to eject it. Drooling occurs. Opening of the jaw is difficult and soft or solid food cannot be taken. Even water is swallowed with the greatest difficulty. Consequently, prostration is marked and emaciation is rapid. The glands on the affected side of the neck are large and tender. Swelling of the palate makes speech difficult and gives the voice a gutteral or nasal quality. If pus collects below the tonsil, respiration may be seriously impeded by edema of the laryngeal tissues. In such cases the inability to open the mouth is not so marked. If complications do not ensue these symptoms disappear rapidly upon spontaneous rupture or surgical evacuation of the abscess.

Diagnosis.—The diagnosis of peritonsillar abscess is usually based upon the presence of a marked acute swelling of the soft palate above the tonsil. Palpation shows this to be tender, and frequently fluctuation can be detected. The diagnosis is confirmed when incision releases pus. Occasionally a *new growth* in the palate or uvula is mistaken for a quinsy, but

the slow onset of the swelling and the absence of fluctuation after it has existed for a considerable period of time should put the practitioner on his guard. Examination of a section of the tumor provides pathognomonic data. Although a *gumma* in the supratonsillar fossa may resemble a quinsy, the persistence of symptoms after incision, the other signs of syphilis, and a positive Wassermann reaction determine diagnosis.

Treatment.—*Incision* and *evacuation of the abscess* is necessary as soon as it is reasonably certain that pus has formed. In the absence of alarming symptoms, especially those of impairment of respiration, it is advisable to postpone operation until this has occurred, and not to resort to early and indiscriminate incision. Pus usually appears after thirty-six to forty-eight hours, and its presence is usually indicated by marked swelling. It is not necessary to wait for distinct fluctuation. Until the time of incision the patient should be made as comfortable as possible. Enough *morphin* or *codein* should be given to blunt the pain. Locally, nothing is more helpful than *irrigation of the throat* with hot sodium bicarbonate solution (1 teaspoonful to 1 quart of water). The heat relieves the pain and the bicarbonate solution enables the patient to remove the tenacious mucus from the throat. An ice-bag may be applied to the neck. After evacuation of the abscess every means should be employed to build up the patient. When recovery has taken place, removal of the tonsils is advisable, but not within a month after an acute attack. Tonsillectomy, if properly performed, usually provides almost complete immunity from subsequent attacks. Symptoms of obstructed respiration usually demand prompt surgical treatment. Marked chills during or following a quinsy should remind the practitioner that thrombosis of the internal jugular vein occasionally follows this disease.

Adenoids.—Definition.—Adenoids are an overgrowth of the normal lymphatic tissue in the nasopharynx, which usually occurs in childhood, but sometimes persists in adult life. This is associated with hypertrophy of the faucial tonsils, and also of the lymphatic tissue at the base of the tongue (lingual tonsil), and at the lateral aspect of the pharynx behind the posterior pillars.

Incidence.—The modern child is very prone to this condition, especially between two and fourteen years of age. As puberty approaches the adenoids normally disappear. Not infrequently they are seen in nursing infants and occasionally they may be observed in adults.

Morbid Anatomy.—The adenoid is a lobulated mass of lymphatic tissue which hangs down from the vault of the pharynx behind the posterior nares. It is composed of lymphatic cells enmeshed in fibrous tissue and covered with a layer of epithelium continuous with that lining the nasopharynx. This growth is reddish and bleeds easily when touched. It often extends to the posterior wall of the pharynx and into the fossa of Rosenmüller. The mass may be small or so large as to occupy the entire pharyngeal vault and completely block the posterior nares. It is frequently the seat of chronic catarrhal or purulent inflammation, and is often subject to acute follicular inflammation similar to that of acute follicular tonsillitis. Catarrhal changes in the eustachian tube and middle ear often accompany this condition.

Symptoms.—As enlargement of both tonsils and adenoids is frequently observed simultaneously and the effects of the two conditions are identical,

the symptomatology of both will be discussed here. The most important symptom and that which usually attracts the attention of the general practitioner is *mouth breathing*. The patient has a vacant, dull *expression*, which in mild cases is noticed only at night during sleep. The patient *snores*, respiration is irregular, and rest is apt to be disturbed. *Nightmare* is common. Attacks of *croup* and *laryngitis* are caused by the labored respiration and mouth breathing. Certain changes in the *bones* and soft tissues of the face may take place: the nostrils are small, the *alæ nasi* become pinched, the upper lip is thick, and the arch of the hard palate becomes high and narrow. When the condition is neglected the *shape of the chest* frequently becomes abnormal. Osler mentions three types of change: "the pigeon or chicken breast, the barrel chest, and the funnel breast." The *voice* may assume a peculiar nasal twang. Obstruction of the eustachian tubes by the adenoid or actual catarrhal changes in the middle ear itself are apt to impair *hearing*. *Mental changes* are common: the patient is apt to be dull, listless, and unable to concentrate (aprosexia). Changes in the disposition are noticed, and the child is often apt to be irritable and nervous. A peculiar *odor of the breath* is frequently noticeable and the nasal chambers produce thick tenacious mucus, which the patient makes ineffectual efforts to remove. The glands at the angle of the jaw are frequently enlarged. Marked nasal obstruction by enlarged adenoids and tonsils frequently influences the general health profoundly, so that the patient becomes undernourished, development is retarded, and recurrent colds and catarrhal laryngitis are common. The presence of enlarged tonsils and adenoids renders the child more subject to diphtheria and scarlet fever, and always seems to render these diseases more severe.

Diagnosis.—The diagnosis of enlarged tonsils and adenoids is usually easy. In the majority of cases a tentative diagnosis based on general symptoms can be confirmed by inspection of the pharynx. In small children digital examination of the nasopharynx readily determines the presence of an adenoid. This growth is felt as a soft, rounded, or flat mass; it frequently bleeds after examination. The walls of a normal nasopharynx are smooth and firm. By skilful use of the posterior rhinoscope mirror, adenoids can often be readily seen even in small children. The general practitioner should, however, learn to depend on digital examination. Aural examination should not be omitted, for it is frequently possible to make the diagnosis of an adenoid by the appearance of the membrana tympani. A retracted drum membrane which is slightly red and glazed, but in which the normal landmarks are visible, is very suggestive of this condition. Occasionally a large *nasal polyp* projecting into the nasopharynx may resemble an adenoid, but careful digital examination shows such structures to be smooth, more or less peduncular, and to arise from the posterior nares and not from the pharynx. Rarely a retropharyngeal abscess may be encountered, but this is felt as a smooth fluctuating mass on the posterior pharyngeal wall, lower than the normal origin of the adenoid.

Treatment.—In the vast majority of cases the only suitable treatment is removal of the adenoid and complete enucleation of the enlarged tonsils. The beneficial results of this operation are so great and so prompt that unless there is distinct reason for its omission, it is folly to advocate and wait for spontaneous shrinking of the tonsils or disappearance of the adenoid when the general symptoms are marked. In very young children,

if the adenoid is large and the tonsils small and apparently not diseased, removal of the adenoid alone may be advised, but parents should be told that in most cases the tonsils will probably have to be removed later. While a skilful removal of the tonsils and adenoid is comparatively simple, every patient should receive careful preoperative and postoperative treatment. The possibility of hemophilia must be eliminated, and in doubtful cases the clotting time of the blood should be determined. If the thymus is enlarged it ought to be suitably treated before operation. The early stages of lymphatic leukemia, associated with a general enlargement of all lymphatic glands, can be eliminated by careful examination of the blood. The operation should be performed in the house or hospital, not in the doctor's office or clinic, because it is extremely undesirable for the patient to be moved within a few hours. Recovery is quicker when rest in bed continues for a week after the operation than when patients are allowed to get up after a shorter interval.

Occasionally complications follow the operation. The most common is hemorrhage; much less frequent are lung abscesses, general sepsis, and death from status lymphaticus. These complications, however, can usually be avoided. Recently *x*-ray therapy has been advocated instead of surgical removal, but in the general concensus of opinion it is unsatisfactory and unreliable. The author feels that enucleation of the tonsils and complete removal of the adenoid with the minimum amount of trauma offers the only solution to the problem.

Chronic Tonsillitis (*Tonsillar Hypertrophy, Chronic Hypertrophic Tonsillitis*).—The tonsil is frequently the seat of chronic disease in individuals of all ages. The exact predisposing causes are unknown, but probably the anatomical configuration of the tonsil, which varies in each person, and the peculiar individual susceptibility to infection are the chief factors.

Morbid Anatomy.—Chronic infection of the tonsil is usually accompanied by hypertrophy of the lymphoid and connective-tissue elements of that body which increases its size. These tissues become relatively and at times actually more prominent; the crypts are frequently filled with pus or cheesy material, often of an offensive odor.

The chronically infected tonsil is subject to acute inflammation, and adhesions often form between the pillars and the tonsil, sealing the crypts. Cysts and abscesses may thus be formed within the substance of the tonsil. Calculi at times develop after cryptic occlusion. Chronic tonsillar infection is often accompanied by an increase in the quantity of lymphoid tissue in the throat. At times an apparently healthy tonsil undergoes simple hypertrophy, but it is probable that in these cases the infection is too mild to cause any systemic symptoms. The subsequent behavior of many such apparently healthy tonsils, when augmentation of the systemic symptoms leads to their removal, bears out this theory.

Symptoms.—The symptoms of chronic tonsillitis vary considerably with different cases. In some instances the general health is good, and there is no evidence of absorption of the pus or caseous material from the tonsil. The symptoms may result entirely from an increase in the size of the tonsil. There are cases in which there are no systemic manifestations, but symptoms of local irritation, such as mild sore throat, pain in the tonsil, a sense of irritation, and hawking and gagging. These are the cases characterized by frequent attacks of tonsillitis. Finally, there are the cases in which there

are no symptoms whatever of disease in the tonsils, though their removal relieves all systemic symptoms of absorption.

Diagnosis.—The symptoms of tonsillar absorption are no different from those of any other focal infection, and diagnosis must, therefore, depend on the actual pathological condition of the tonsil, the local symptoms, or the acute attacks, and upon exclusion of other sources of infection. Bacteriological examination of the crypts of a suspected tonsil usually demonstrates the presence of *Streptococcus viridans* or *Streptococcus hemolyticus*. This is accepted by some observers as evidence of the cause of general systemic infection, although these organisms are frequently present in the tonsils of persons without general systemic disease. Nevertheless, suspicion should be aroused when a virulent hemolytic streptococcus can be obtained from the tonsil in pure culture.

Treatment.—In certain cases of chronic tonsillitis with mild local and systemic symptoms temporary relief may at times follow *evacuation of the tonsillar crypts* either by suction or by the application of gentle pressure on the tonsil. Minor operations on the tonsils, such as slitting the crypts or their obliteration with the galvanocautery, are advocated by some, but a more thorough operation is usually necessary in the end. *Tonsillectomy* is the only surgical treatment worth consideration, and should be performed whenever the local symptoms are marked, or when it seems fairly certain that the tonsil is the cause of symptoms. *x-Ray therapy* should be used only when operation is distinctly inadvisable. Its efficacy is questionable.

T. Laurence Saunders.

Diseases of the Esophagus

Although diseases of the esophagus occur in only a fraction of 1 per cent. of the cases treated in the wards of a general hospital or its outpatient department they are important, because in many instances they cause some obstruction to the passage of food into the stomach. With complete obstruction, starvation occurs in spite of attempts to keep up nutrition by artificial feeding. As certain of the obstructions are curable, it is especially important that an accurate diagnosis be made so that appropriate treatment may be recommended.

Methods of Examination.—Very little information in regard to the esophagus can be obtained by palpation, auscultation, or the other simpler methods of examination on account of its position, and therefore special diagnostic methods must be used. Fortunately, the esophagus can be quite accurately studied by means of the Roentgen ray, so that a very satisfactory diagnostic procedure is available for the average physician. Although it is very easy in this way to detect irregularities of its walls, it is not so easy to determine the character of the pathological process. By far the most satisfactory special method for studying the esophagus is direct inspection through the *esophagoscope*. It is possible to pass a straight tube into the esophagus so that direct inspection may be made. This may be done without the use of an anesthetic, if the patient will co-operate.

In order to obtain satisfactory results with the esophagoscope special technical skill is necessary which can only be acquired after considerable practice. Therefore the esophagoscope is not an instrument which can be used by practitioners in general, and its usefulness is accordingly somewhat limited. Before an important decision is made in regard to obscure disease of the esophagus, however, a direct inspection by someone skilled in this work should be insisted upon in addition to the *x*-ray examination. Examination of the esophagus by sounds passed directly or along a previously swallowed string is of some value, but this method of study is being superseded by the use of the Roentgen ray and direct inspection.

Congenital Abnormalities of the Esophagus.—As most of the congenital abnormalities of the esophagus cause complete obstruction or are associated with a fistulous opening into the trachea or bronchi, the subjects quickly succumb to starvation or pneumonia. Therefore these problems are of no practical importance to the physician. There is one type of congenital abnormality in which the obstruction is produced by a fold of the mucous membrane which extends across the lumen, a so-called esophageal web. It is possible to rupture this web and re-establish communication between the mouth and stomach. This should be followed by dilatation with a bougie at certain intervals in order to prevent contraction of the lumen of the esophagus as the mucous membrane heals. Congenital dilatations and narrowings of the esophagus without symptoms are reported; or symptoms may develop only after many years.

Diverticulum of the Esophagus.—Esophageal diverticula are usually divided into two groups: the traction and the pressure diverticula. The former are the result of some distortion of the esophagus by the pull of the contracting scar tissue in some adjacent cicatrizing process, and, as a rule, are not of any clinical importance. The latter are usually actual herniæ of the mucous membrane of the esophagus through the muscle layers of the wall, although in rare instances all the coats of the esophagus may be included in the pouch. Actual hernia of the mucous membrane of the esophagus is apt to occur at two special points: at the junction of the pharynx and esophagus where the muscle coats do not completely surround the tube, and at the narrowing of the esophagus caused by the pressure of the left bronchus as it crosses in front of the esophagus. These pressure diverticula are also apt to occur where the wall of the esophagus has been weakened by disease or trauma. The opening into the diverticulum may be small or large and the pouch may reach such size that it produces a very definite tumor mass, which can be felt in the neck if the diverticulum is high up in the esophagus. The pouch may be so situated that when it is filled with food it impinges upon the lumen of the esophagus and actually causes obstruction to the passage of food.

The *symptoms* caused by a diverticulum depend upon the size of the diverticulum and the quantity of food held within the pouch. Decomposition of the residual food causes foulness of the breath and dryness and irritation of the mucous membrane in the pharynx. There is usually an excessive secretion of mucus. The food which may be regurgitated from the sac does not contain free hydrochloric acid. Difficulty in swallowing occurs in certain cases, especially when the pouch becomes distended and presses upon the esophagus.

Upon *physical examination* it may be possible to feel the tumor mass in

the neck on one side or the other of the esophagus if the diverticulum is situated high up. A tumor mass in this region which is present at times and disappears after regurgitation should suggest an esophageal diverticulum.

The *diagnosis* can be readily confirmed by the Roentgen-ray examination, for the opaque substance appears in the sac outside of the usual course of the esophagus.

The *treatment* of diverticula of the esophagus varies with their location and character. If the diverticulum is outside of the thorax it should be removed by surgical procedure. If so situated that it cannot be removed, operative procedures may be employed in favorable cases to enlarge the opening into the pouch so that food will more readily pass out of it. This operation, of course, is dangerous unless there are definite adhesions between the wall of the esophagus and the wall of the pouch. In certain suitable cases the symptoms may be relieved by washing out the pouch once or twice a day. Great care must be used in any sort of instrumentation because it is very easy to rupture the sac if force is used.

Inflammations of the Esophagus.—Lesions may occur in the esophagus during the course of many of the acute infections, such as the eruption of smallpox, the ulcers of typhoid fever, the ulcers of tuberculosis, and the reactions associated with infection with glanders, actinomycosis, etc. The diphtheritic membrane may extend into the esophagus, and a primary syphilitic lesion has been reported. Usually, however, these lesions are masked by the other symptoms of the disease and are, therefore, of very little practical importance to the clinician. Acute inflammation, on the other hand, may be produced in the esophagus by chemical irritants or pus-forming organisms. These inflammatory agents may reach the esophagus from the mouth or extend to it from inflammation in adjoining structures. A less acute inflammatory reaction which produces a catarrhal condition of the esophagus may be produced by the action of less severely irritating substances over a longer period of time.

Symptoms.—Acute inflammation causes pain along the course of the esophagus which becomes pronounced on swallowing, and, in addition, often difficulty in swallowing, and a marked increase in the excretion of mucus in the pharynx and mouth. Vomiting may occur, and the vomitus will be mixed with mucus and blood. Extreme thirst is a common symptom. Should the inflammation become so severe that rupture of the esophagus occurs, the patient will show marked prostration and localized symptoms dependent upon the structure into which the rupture occurred. There may, of course, be general constitutional symptoms and a febrile reaction proportional to the severity of the infection.

Diagnosis.—A history of swallowing some irritating substance is an important aid in diagnosis. It is undesirable to use instruments blindly in an esophagus which is acutely inflamed for fear of rupture. Roentgen-ray studies are usually not indicated. If the diagnosis is not satisfactory, careful inspection with the esophagoscope may be tried.

Treatment.—The treatment of acute inflammations of the esophagus consists in removing the irritating causes and in giving the esophagus as complete rest as possible. Oil or cool drinks may be administered by mouth, but food should be avoided for several days. The fluid content of the body can be kept up by the introduction of fluid in other ways if the

swallowing of cool drinks is too painful. An ice-bag brings comfort when applied to the esophagus above the thorax.

The possibility of stenosis of the esophagus after healing of the acute inflammation must be remembered, for it may lead to definite obstruction. It is important to diagnose obstruction early before dilatation of the esophagus above it has occurred. An esophagus may dilate markedly; indeed, in one case a dilated esophagus held 1800 c.c. The treatment for this type of obstruction consists in dilatation of the stenosed area by bougies of various sizes which are gradually passed through the stricture directly or along a previously swallowed silk thread.

Ulcers of the Esophagus.—In bedridden or uremic patients, or in patients in whom there is some external pressure upon the esophagus, the mucous membrane is apt to ulcerate. The ulcers are of little clinical importance because the symptoms they produce are overshadowed by other processes. Ulcers occur in the esophagus, however, which are similar in character to the so-called *peptic ulcer* of the stomach; and may be associated with similar ulcers in the stomach or duodenum, or be quite independent of them. These ulcers may exist without causing any important symptoms. On the other hand, there may be pain and difficulty upon swallowing, and in some cases regurgitation of food. Hemorrhage may be an early symptom and may be severe. The ulcers may perforate into the adjacent tissues and produce death in this way. A case has recently been described in which the pain suggested that of angina pectoris.

Diagnosis without the use of the esophagoscope may be difficult, for the Roentgen ray may not demonstrate the ulcer. The treatment of such an ulcer is similar to that of a peptic ulcer in the stomach. Local applications may be made through the esophagoscope, but their value is uncertain.

Spasm of the Esophagus.—Spasm may occur at any point in the esophagus, but usually takes place at the lower end. It is then spoken of as cardiospasm. In *cardiospasm* the muscle-fibers of the diaphragm may play an important part. Spasm may occur without any demonstrable disease of the esophagus, or at one point in association with ulceration or inflammation of some other part of the tube. Spasm of the esophagus may occur at any age; it may last for a short time or a period of years; and may let up and gradually allow food to pass into the stomach, or persist until eventually the food in the esophagus is regurgitated. The esophagus may be markedly dilated as a result of simple cardiospasm.

Symptoms.—The symptoms are sudden difficulty in swallowing, which may or may not be associated with pain in the thorax or throat. Vomiting may be the first manifestation noted by the subject. If the esophagus is dilated, the vomiting may not occur immediately after the meal, but only after some hours. The patient may know just when the spasm relaxes.

Diagnosis.—The condition must be separated from obstruction due to organic disease. The Roentgen-ray examination usually establishes the diagnosis by revealing the deformity in the esophagus above the stricture in new growth, and the intermittent character of the obstruction in spasm. An absolute diagnosis, however, cannot always be made by the Roentgen ray, and in doubtful cases an examination with the esophagoscope is necessary. It should be remembered that spasm may be superimposed upon organic disease.

Treatment.—The treatment consists in dilatation of the spastic area.

This is usually done under a general anesthetic with special care to avoid rupturing the esophagus. Although a single dilatation may sometimes cure the condition, several treatments may be necessary. The spasm may return after several years. In addition to the local treatment it is important to study the patient carefully in order to eliminate any other physical or mental disturbances which might produce reflex spasm. If considerable dilatation of the esophagus has taken place, the result from dilatation of the spastic area is less satisfactory, and care must be exercised not to overload the esophagus after the spasm has been relieved.

Tumors of the Esophagus.—Both benign and malignant tumors of the esophagus occur. Carcinoma is the most common type; in fact, primary carcinoma of the esophagus comprise about 7 per cent. of all the carcinomas found at autopsy. Fibromas, papillomas, and accessory thyroid tumors have been observed in the esophagus, and also diffuse fibromyomata involving practically the entire musculature of the tube. Cysts also develop in the wall of the esophagus. These benign tumors are usually of no importance unless they attain sufficient size to obstruct the lumen. After they have become disturbing, attempts to remove them through the esophagoscope should be made if they are operable.

Carcinoma of the esophagus is more common in men than in women. It is usually situated at one of the three natural narrowings of the esophagus: at its start, where the left bronchus crosses in front of it, or at the point where it passes through the diaphragm. The lower end of the esophagus is more apt to be the site of the new growth.

Symptoms.—The most common initial symptom is increasing difficulty in swallowing, usually without pain. Pain in the epigastrium is a fairly common initial symptom, and loss of appetite or belching of gas and hiccups have been reported to be the first symptoms noted. As the disease progresses signs of starvation gradually develop. The patient loses weight rapidly, and constipation becomes prominent on account of the small amount of food eaten. Thirst is very distressing if the obstruction is complete. Hemorrhage may occur if ulceration is present. The blood may appear in the vomitus or only as tarry stools. If carcinoma of the esophagus is suspected it is well not to pass the stomach-tube for fear of hemorrhage or even perforation.

Diagnosis.—The diagnosis can usually be made by means of the Roentgen ray, but if there is doubt as to the nature of the obstruction, direct inspection should be made by the esophagoscope.

Treatment.—At the present time carcinoma of the esophagus should be regarded as a fatal disease, and therefore surgical intervention as a curative measure need not be considered except in especially favorable instances. The Roentgen ray or radium may delay the growth of the tumor or temporarily diminish the obstruction, but the results of such treatment are, on the whole, unsatisfactory, unless the tumor happens to be at the upper end of the esophagus where radium can be more readily applied. Feeding the patient through a gastrostomy opening may prolong life for a certain length of time, but only under conditions which are of doubtful pleasure for the patient. Of course, individuals vary in their feelings in regard to prolonging life under these circumstances. By careful dilatation of the esophagus at the site of the growth complete obstruction can be somewhat postponed. If the obstruction becomes complete, the distressing

thirst can be relieved by the introduction of fluid into the rectum, a vein, or under the skin. Opiates should be liberally employed as the disease progresses. Attempts to prolong life by rectal feeding are, on the whole, unsatisfactory.

Neuroses of the esophagus may be either sensory or motor and are associated with other signs or symptoms suggestive of an unstable nervous equilibrium. Of course, careful examination should be made to rule out organic disease. The *sensory disturbances* along the esophagus are varied, and usually consist in some discomfort in swallowing, although they are not associated with difficulty in the passage of the food into the stomach. The *motor neuroses* consist of spasm of the esophagus, which has already been mentioned, and the so-called *globus hystericus*. This is considered by some to be a mild spasm which passes along the muscle coats of the esophagus, and by others to be a contraction of the cricopharyngeus muscle. There is no specific local treatment for neuroses of the esophagus.

Esophageal Varices.—Dilatation of the veins in the esophagus is common if there is any obstruction to the return of blood through either the inferior or superior vena cava or through the portal circulation, because the veins of the esophagus empty into all three and anastomose with each other. The most common cause of dilatation of the veins of the esophagus is cirrhosis of the liver. The dilated veins may not produce any *symptoms* or they may rupture and cause a sudden unexpected hemorrhage. Attempts to decide upon the cause of the unexpected hematemesis should not be made until the bleeding has entirely ceased, and then blind instrumentation should be avoided. As the Roentgen ray will very likely fail to demonstrate the varices, examination by the esophagoscope may be necessary for diagnosis.

There is no *specific treatment* for dilated veins in the esophagus.

Rupture of the Esophagus.—The esophagus may be ruptured by the trauma from a foreign body, and also by severe vomiting or the passage of large pieces of food, but it is possible that in these cases there has been in addition some unrecognized disease of the wall. Rupture is followed by the signs and symptoms of collapse, and leads rapidly to a fatal termination, with the symptoms pointing toward the site of the rupture. The diagnosis is readily made by means of the Roentgen ray, which will show barium passing outside the lumen of the tube. Up to the present time surgical treatment of rupture of the esophagus has not been successful.

Foreign Bodies in the Esophagus.—A foreign body may lodge in the esophagus without producing symptoms, or very rapidly produce symptoms of obstruction. In children, in addition to the difficulty in swallowing, there may be definite interference with respiration. The history, of course, is an important aid in making the diagnosis. The Roentgen ray may demonstrate the foreign body either directly, when it casts a direct shadow, or by a defect in the barium shadow if the foreign body itself does not obstruct the rays. Sometimes the foreign body cannot be detected while the barium is being swallowed, but may be revealed by the barium which adheres to it after the barium has reached the stomach.

A foreign body should be removed with the aid of the esophagoscope as soon as the diagnosis is made. Attempts to push a foreign body into the stomach or the blind removal of a foreign body from the esophagus without first inspecting are dangerous. CHANNING FROTHINGHAM.

Diseases of the Stomach

DYSPEPSIAS

The majority of digestive disorders are not the result of definite organic lesions, but of functional disturbances (motor, secretory, sensory), and are usually termed "dyspepsias." They can be rather roughly divided into three types: the primary, which, in the main, results from faulty habits of eating and drinking; the nervous, which is psychogenic; and the secondary, which is a reflex disturbance consequent to disease elsewhere in the body. The term *gastritis* should probably be applied to conditions in which there is definite evidence of inflammatory change, and the term *dyspepsia* to the large group of disturbances in which there is no appreciable disease of the organ to account for the symptoms.

Primary Dyspepsia.—The fundamental cause of primary dyspepsia is not an inherited or acquired instability of the nervous system, but such physical factors as dietetic errors, rapid and careless eating, poor mastication of food, and poor choice of food and drink. The stomach often retains its normal function notwithstanding such strain, but a few individuals, sooner or later, show definite signs and symptoms of true gastritis, and many respond, eventually, to the repeated trauma by functional abnormalities such as hyperacidity or subacidity, and increased motor activity or sluggishness. These are followed by the usual symptoms—fulness and distention after eating, especially after heavier meals, epigastric discomfort, eructation of gas, heart-burn, constipation, coating of the tongue, loss and fickleness of appetite, and often somnolence after meals, headache, and lassitude.

The *treatment* of these conditions is the basis of their classification as a separate group. By eliminating the faults of living and eating it is possible to cure these patients. Treatment consists in the establishment of regular hours for meals; insistence upon leisurely eating; the elimination from the diet of indigestible foods (fried and greasy foods, the inside of hot breads, pies and pastry, sweets, condiments, alcohol, often coffee, and very hot or cold foods), especially if the individual is fatigued; maintenance of suitable oral hygiene; and establishment of a mode of life which permits plenty of exercise, exposure to fresh air, and diversion and sleep. As in the treatment of all digestive diseases, these principles must be persistently followed, for with return to bad habits, symptoms sooner or later reappear.

Nervous Dyspepsia.—The gastric neuroses, protean polysymptomatic nervous dyspepsia, and what may be called the monosymptomatic type, constitute a very large proportion of gastric disturbances. They may be defined as conditions associated with no demonstrable disease of the stomach, or with disease which is secondary to the primary functional disturbance. The cause is congenital or acquired irritability or asthenia of the nervous system, an abnormal psyche, and hyperesthesia or paresthesia of the portion of the vagus and sympathetic which supplies the stomach. Many cases are entirely or almost entirely psychogenic. Often signs of hyperexcitability of other branches of the vagus or sympathetic, such as those supplying the heart or the intestine, are noticeable. Usually there are manifestations of psychic instability in other viscera, but in some in-

stances the gastric symptoms occur alone. Frequently, the gastric syndrome predominates so distinctly as to justify independent consideration, but the underlying psychic instability must *always* be regarded as of fundamental importance in therapy.

Polysymptomatic nervous dyspepsia is a mixed neurosis which is practically always psychogenic. The character of the gastric disturbances changes frequently and there are usually psychasthenic manifestations elsewhere in the body—fatigue, headache, poor circulation, palpitation of the heart, a congested feeling in the head, dizziness, signs of worry or anxiety, inability to concentrate, and easy fatiguability. The digestive system is so hyperesthetic that many of its functions rise above the threshold of consciousness. The patient complains of the usual dyspeptic symptoms—burning epigastric sensations, nausea, sometimes vomiting, fulness and discomfort, a feeling of pressure behind the sternum or in the epigastrium; eructation of gas, and sometimes difficulty in swallowing (a globus of hysterical origin). The appetite is often poor. In certain cases, an accessory sitophobia results from the belief that an ever-increasing list of foods is responsible for the discomfort. This often causes marked loss of weight, although frequently the appetite is either normal, variable, and capricious, or even increased. Some patients think that only in hyperalimentation can they recall health. Although the syndrome changes frequently, there is no periodicity of symptoms and no definite relationship between quality and quantity of food and gastric discomfort. Sometimes anything can be eaten with impunity, while at others the simplest foods, or even a glass of water, may cause discomfort or intense subjective pain. The symptoms are peculiarly dependent on the psyche. Diversion or entertainment often entirely cures them; and worry, distress, or anxiety aggravates them.

Diagnosis is, as a rule, not difficult, although every patient requires the most careful general and special observation. Organic disease of the stomach or other organs must first be excluded and the patient persuaded that the condition has no organic basis. The protean picture, its kaleidoscopic changes, its association with other signs, symptoms, or stigmata of psychasthenia or neurasthenia; the patient's susceptibility to outside influences and to suggestion; and the absence of organic disease should permit diagnosis. It must, however, always be remembered that psychasthenic individuals are not immune to organic disease, and that because of hyperexcitability the functional disturbances always produced by organic disease are often so exaggerated as to obscure entirely the organic lesion. Consequently a diagnosis of functional psychogenic dyspepsia is never justifiable until after the most thorough examination of the entire body. Even if marked improvement or apparent cure follows treatment for the psychogenic disturbance, an organic lesion may be present.

The *treatment* is fundamentally upbuilding and re-educational and should be so devised as to demonstrate to the patient the lack of basis for his belief that there is an organic lesion. The diet should be general and mixed even when there is bitter complaint that it will produce discomfort. It is important not to yield to every whim, and also to sympathetically explain to the patient why his preconceived ideas of diet are unsuitable. Reasoning, persuasion, and encouragement are necessary to overcome the difficulties which are inevitable at the beginning of such treatment. The patient

must have both confidence in the doctor and respect for his authority. Rest is often invaluable at first; and occupational therapy, selected exercise, a change of scene or occupation, forced feeding if the patient is undernourished, massage, fresh air, long hours of sleep, and a cold morning shower or sponge if the patient reacts well are also beneficial. For entirely successful treatment the patient must attempt to look at himself through the doctor's eyes. Cure may be only temporary, for certain individuals are always subject to relapse if re-exposed to the influences which caused the primary attack. Full appreciation of the true nature of the disturbance minimizes this susceptibility.

The GASTRIC NEUROSES are frequently divided into the hypersthenic and hyposthenic types; the former characterized by hyperperistalsis, hypersecretion, and hypersensitiveness, the latter by sluggish motor and secretory activity. In some ways this is a very satisfactory classification, but since there are so many variations from these two types in which one function is increased and another decreased, or one alone changed, it seems wiser to consider the functional motor, sensory, and secretory abnormalities separately. It is convenience and not scientific accuracy which justifies this, because the various functions are very closely related.

SENSORY NEUROSES (1) *Bulimia* (*Hyperorexia*).—Bulimia is an increased sensation of hunger which is usually associated with various organic diseases, such as ulcer, chronic gastritis, diabetes, hyperthyroidism, etc. It may also be a pure neurosis or accompany hysteria. Sometimes patients with this disturbance derive no satisfaction from eating; and polyphagia, often of a paroxysmal type, consequently develops. The *treatment* is fundamentally that of the underlying cause. If this is purely psychic, suggestive therapy and administration of bismuth, the bromids, or anesthesin are desirable.

(2) *Anorexia* (*Loss of Appetite, Anorexia Nervosa*).—Anorexia is often constant, and may persist for such long periods as to cause great emaciation. As it is a depressive phenomenon, the *treatment* should be stimulating. Optimistic psychotherapy, surroundings with plenty of fresh air and cheer, sometimes forced feeding (occasionally through a stomach or duodenal tube), and administration of bitters, especially nux vomica in increasing doses or orexin tannate, are helpful.

(3) *Hyperesthesia of the gastric mucosa* is sometimes a pure neurosis, but is more often associated with organic disease. It is essentially an abnormal sensitiveness to various stimuli and only rarely develops during fasting. This probably explains the great differences in the severity of the pain in different individuals with identical lesions. In *treatment* the general measures, as well as administration of bismuth in very large doses, or of belladonna and the bromids, often in combination, are most successful. Nitrate of silver ($\frac{1}{4}$ to $\frac{1}{2}$ grain after meals) sometimes gives relief, but it should not be given for long periods on account of the danger of *argyria*. Sometimes Hoffmann's anodyne, chloroform-water, aspirin, or anesthesin are helpful.

(4) *Gastralgia* (*Cardialgia*).—True gastralgia is only rarely of purely nervous origin, and while it may be a neurosis, is usually caused by organic disease. It may be defined as severe paroxysmal pain in the stomach which is often preceded by dyspeptic disturbances. It may last for a shorter or longer period, is occasionally persistent, and often recurs only

after long intervals. The *diagnosis* of purely neurotic gastralgia should never be made, even when there are other signs of neurasthenia or psychasthenia, until all possibility of organic disease has been ruled out. Gastric or duodenal ulcer, acid gastritis, carcinoma (rare), angina pectoris, renal and biliary calculus, chronic appendicitis, pancreatic disease, floating kidney (rare), pyelitis, intestinal parasites, epigastric hernia, severe malaria, organic disease of the central nervous system (tabes, myelitis, multiple sclerosis, and brain tumor) are the most probable causes; and gout, nephritis, and other forms of toxemia may possibly produce such symptoms. Treatment for the gastralgia *per se* consists in the application of an ice-bag or hot compress and institution of the therapeutic measures suitable for hyperesthesia. If the pain is very severe, administration of morphin or pantopon may be necessary, but, as a rule, it is unwise to administer opiates until the cause of the pain is ascertained.

Motor Neuroses.—The motor function of the stomach is so affected by the emotions that after any emotional stress peristalsis may completely cease. Certain types of acute indigestion are undoubtedly caused by this, but of all the motor disturbances, psychogenic atony is the most important. The upsets of many psychasthenic patients are due in some measure to such atony which prolongs the emptying time of the stomach. *Nervous eructations* may be associated with this condition, but usually occur independently. They almost always result from the swallowing of air (aërophagia) which is a true motor neurosis. The symptoms may be purely nervous or associated with gastroptosis, atony, and secondary dyspepsia, espepecially that accompanying disease of the gall-bladder. In *diagnosis*, the relatively rare increase in the fermentation of the stomach contents which occurs, especially in atonic dilatation of the stomach and in pyloric obstruction with secondary gastrectasy, must be differentiated. Aërophagia is a veritable tic which is a common cause of epigastric discomfort, gastric distention, and eructation. The gas is usually odorless and tasteless. The condition should be treated mainly by re-education and employment of general measures which improve the physical and psychic condition—tonics, exercise, cold baths. Sometimes bromids are helpful. To prevent the excessive swallowing of air a string or ribbon may be tied so tightly about the neck as to cause discomfort whenever air is swallowed. This demonstrates to the patient the cause of trouble, and is a constant reminder of the necessity of breaking the habit.

Regurgitation is the unconscious or sometimes conscious return of food into the mouth from the stomach without nausea or vomiting. It is probably caused by paresis of the cardia and antiperistalsis of the stomach. Although true *nervous vomiting* is not rare, and may occur after severe shock, especially in nervous individuals, most vomiting is not of nervous origin. Other causes are brain tumor, which is associated with vomiting without apparent cause; tabes which sets up intractable vomiting without pain; myelitis; cholelithiasis; renal calculus; floating kidney; fecal impaction; intestinal parasites; strangulated hernia; pregnancy, which should always be considered a possible cause in nervous women; retroflexion of the uterus; peritonitis; drugs; and often various infections and intoxications. If all of these are eliminated and vomiting begins after a sudden shock or long strain, it is presumably nervous. No secretory disturbances accompany this syndrome and often no nausea. Between attacks, the motor function

is usually normal. In children, periodic vomiting which may be very severe and intractable, and appears to be nervous, probably results from a toxemia with disturbed hepatic function (cyclic vomiting). The etiological rôle of hypersensitiveness to certain foods must always be considered. Pain is not a common symptom. Usually the attacks are transient and require no special *treatment*, but nux vomica, tincture of iodin, menthol, or cerium oxalate may be administered if the vomiting persists or recurs. The usual measures to quiet the patient and restore his morale should, of course, be employed.

Hyperkinesis (peristaltic unrest of the stomach) may be of purely nervous origin. It is readily demonstrated by the fluoroscope, and is almost always produced by conditions which obstruct the pylorus or by reflex pylorospasm resulting from disease in other parts of the body.

Secretory Neuroses.—Since the introduction of the stomach-tube, investigations of the pathology of the stomach have become largely studies of the chemical function alone. Unfortunately, the methods employed, even the more refined fractional methods, involve so many sources of error, and are in so many respects unphysiological, that the conclusions based thereon can at best be only rough. They are never an exact picture of the secretory activities of the stomach. It is also more and more appreciated that it is the motor, not the secretory disturbances that play the larger rôle in the production of symptoms. Although secretory studies are essential in a small proportion of cases, and helpful in many others, complete dependence upon them in diagnosis leads to many serious mistakes. The correlation of data thus obtained, however, with the *x*-ray findings and history provides the best means of obtaining a correct conception of the underlying pathological process. All types of secretory anomaly —hypersecretion, hyposecretion, and achylia—may be psychogenic; but persistent hypersecretion, even if of purely psychic origin, unquestionably produces, in time, very definite changes in the acid-forming apparatus which must be considered organic lesions. Secretory anomalies are sometimes associated with motor and sensory disturbances. Hyperesthesia and hyperperistalsis are often associated with hypersecretion (hypersthenic dyspepsia), while with hyposecretion, sluggish peristalsis and decreased irritability are not an unusual combination (hyposthenic dyspepsia). There are, however, many exceptions to this, such as the achylia accompanied by hypermotility and hyperesthesia.

(1) *Hypersecretion* (*hyperacidity*, *hyperchlorhydria*) is secretion of an increased quantity of acid by the gastric glands. This is accomplished not by concentration of the gastric juice, which normally contains about 0.5 per cent. acid, but by the production of a larger quantity of fluid. The term *hypersecretion* is, therefore, the most accurate. *Hyperchlorhydria* is merely hypersecretion after ingestion of food. *Continuous hypersecretion* is the term applied when acid is secreted after ingestion of food and during fasting as well.

These conditions indicate an abnormal irritability of the glandular apparatus which is usually of psychic origin, but may be confused with the reflex hypersecretion caused by disease. The more thorough the observation of patients, the larger becomes the proportion of cases of reflex origin which follow chronic appendicitis, chronic constipation, renal and ureteral calculus, diseases of the genitalia, intestinal parasites, etc. Pyrosis, ful-

ness and discomfort from one to three hours after meals, and acid eructations are the usual *symptoms*. These are aggravated by acid or irritating foods, and by worry or strain. As a rule, the appetite is good and there is no marked disturbance of the general nutrition. *Diagnosis* depends upon the presence of psychasthenic manifestations, the high acid-content of the stomach after the test-meal, or in the fasting stomach (the free acid over 40; the total acid between 70 and 110), and the absence of organic disease which might reflexly produce these changes. *Acid gastritis* may be distinguished by the presence of considerable gastric mucus; *ulcer*, by the characteristic *x*-ray picture, the presence of occult blood in the stools, and usually by the marked periodicity of symptoms. A thorough general physical examination eliminates the possibility of reflex hypersecretion.

Treatment.—The underlying neurosis should be treated by the usual methods—re-education, re-adjustment, and upbuilding—as well as by other measures. The *diet* must be non-irritating and contain at first no condiments or coarse foods, especially coarse raw fruits. As a rule, alcohol, tobacco, coffee, and salt should also be avoided. The ingestion of large amounts of butter and cream (fats) materially decreases the secretion of acid. Milk, eggs, cereals, purée of green vegetables, and the simpler meats, if well borne, may be given, but in some cases the starch intake must be reduced. The most useful drugs are belladonna (large doses before meals) and alkalies, especially a combination of the lighter (bicarbonate of soda) with the heavier (calcined magnesia, calcium carbonate, bismuth subcarbonate). A visit to Vichy, or Vittel or Neuenahr not only makes available alkaline drinking-water, but also furnishes the change of environment which is so often helpful.

Most *continuous hypersecretion* is of organic and not of psychasthenic origin, but should be treated like other types of hypersecretion except that the organic cause must be eliminated. The patient must be made to realize the nature of his condition, for without such knowledge, and confidence in his physician, the co-operation essential to successful treatment is impossible.

(2) *Hypo-acidity* (*subacidity, hypochylia, anacidity, achlorhydria, achylia*) is, in a sense, a depressive neurosis which may be periodic or constant. It is very frequently associated with mental fatigue, and persistent worry and strain, especially in individuals with a congenitally unstable psyche. The condition may be congenital when the glandular apparatus is normal and the proper psychic stimuli are lacking. Although frequently the disturbance is purely psychogenic, it is often associated with general or local organic disease, such as gastritis, long febrile or wasting diseases, congenital myasthenia, and anemia. These must all be proved absent before the *diagnosis* can be established.

The *symptoms* are very vague. Lack of appetite, a feeling of fulness after eating, absence of pain, eructations of gas, sometimes constipation, and sometimes diarrhea, especially with achylia—true psychogenic gastrogenous diarrhea which is immediately relieved, as a rule, by hydrochloric acid therapy—are the most marked manifestations.

The *treatment* should build up the patient, relieve worry and strain, reduce mental and physical fatigue, establish ingestion of a stimulating diet with plenty of acid foods (acid fruit juices, buttermilk, *Bacillus acidophilus* milk, etc.), and provide adequate medication. Strychnin may be given in

large doses, and cacodylate of soda or iron injected hypodermically. A holiday in a bracing climate, massage, increasing exercise, sometimes preceded by rest and occupational therapy, may all be helpful. Hydrochloric acid is not usually of benefit except in the treatment of achylia with diarrhea. Orexin tannate is often used to increase the appetite, but the ordinary bitters, such as gentian and cinchona, are just as satisfactory.

(3) *Gastromyxorrhea* is excessive secretion of gastric mucus. It is purely neurotic and not accompanied by inflammation. The condition is most often seen in neurotic or hysterical young girls with the stigmata of visceroptosis. *Diagnosis* depends on the neurotic or hysterical substratum, the presence of a large amount of pure gastric mucus in the stomach after the test-meal and during fasting, the lack of inflammation, and the absence of demonstrable organic disease. The symptoms appear periodically after great emotional strain. The *treatment* is that appropriate to the underlying neurosis or hysteria, and in the more marked cases may include a short course of gastric lavage.

Secondary Dyspepsia.—Every acute and chronic disease may in some part of its course cause gastric symptoms. These may be slight, transient, and purely functional, or severe, persistent, and productive of organic change.

Acute Infections and Intoxications.—Practically all infections and intoxications are associated with functional gastric disturbances, and occasionally with organic disease as well, especially acute gastritis and gastric erosion. Sometimes these *symptoms* are most marked in the prodromal stage. They are usually of no especial significance and cease shortly after, or even before, other symptoms of the disease disappear. Anorexia, nausea, vomiting, a sensation of fulness, eructations, epigastric discomfort, and heart-burn are the most common. In a few cases, however, the symptoms persist for some time after the underlying disease has been completely cured, as, for example, the subacidity or achylia with atony which often follows typhoid fever.

Diseases of Other Abdominal Organs.—Most diseases of the abdominal viscera cause gastric symptoms; indeed, these may be the only manifestations. The gastric symptoms of acute and chronic appendicitis, gall-bladder disease, epigastric hernia, inguinal hernia, or peritoneal adhesions of whatever origin are very striking, and often are so predominant as to divert attention completely from the underlying lesion. Usually the pain of the pylorospasm and the discomfort produced by hyperacidity are the striking symptoms; but in chronic gall-bladder disease, especially chronic cholelithiasis, dyspepsia with fulness, gaseous distention, eructations, and subacidity or achylia are the most noticeable symptoms. When ulcer is not the cause of periodic dyspepsia, an extragastric etiology should be suspected. The history of previous attacks, a thorough physical examination, and *x*-ray studies usually permit correct diagnosis. The flatulent dyspepsia of women forty or fifty years of age who have borne children is often due to unrecognized disease of the gall-bladder. Frequently the syndrome typical of an ulcer is a reflex manifestation of chronic appendicitis. Constipation and various intestinal parasites can produce, in a mild form, the symptoms of acid dyspepsia with pylorospasm.

Circulatory Diseases.—The onset of *myocardial decompensation* is frequently first demonstrated by gastric discomfort, fulness after meals,

and gas. These are purely functional at first, but eventually a true gastritis may develop. Rest and digitalis will often quickly give at least temporary relief. Exercise and treatment of the gastric condition *per se* may do great harm. *Arteriosclerosis* sometimes manifests itself as a purely gastric disorder in which atonic dyspepsia or attacks of epigastric pain are the most striking features.

Pulmonary Tuberculosis.—One of the commonest early symptoms of *pulmonary tuberculosis* is a functional dyspepsia. This is sometimes combined with inexplicable psychasthenic manifestations, and by either an increase or decrease in the secretion of hydrochloric acid. Occasionally there is bulimia, but usually a marked anorexia develops.

Diseases of Metabolism and the Endocrinopathies.—*Gout* is commonly associated with banal dyspeptic symptoms and achylia is the rule. Hydrochloric acid is often a more successful therapeutic agent than the alkalies usually employed.

Bulimia is a common manifestation of *diabetes.*

In both *hyperthyroidism* and *hypothyroidism* achylia usually appears. In the former, it is often associated with gastrogenous diarrhea; in the latter, with intractable constipation.

True *gastric crises* sometimes occur in *Addison's disease.*

Anemia.—In *chlorosis* and *secondary anemia* dyspeptic symptoms are often associated with functional subacidity and slight atony. The gastric symptoms of *pernicious anemia,* on the other hand—nausea, vomiting, anorexia, and achylia—are probably evidence of organic disease of the stomach.

Renal Diseases.—Diseases of the kidneys are likely to be strikingly manifested by gastric symptoms. In fact, these may be the only evidences of renal disease. Attacks of nausea, vomiting, and epigastric pain are caused by a *floating kidney* (Dietl's crises), and *renal* and *ureteral stones* produce a somewhat similar syndrome. In certain cases of *pyelitis* and *ureteral stricture* this is also true, but the symptoms of nephritis are usually referable to a secondary gastritis, the etiology of which is probably both toxic and circulatory. Sometimes multiple superficial ulcers develop. Renal disease should, therefore, be considered the possible cause of dyspepsia of unknown etiology in middle-aged individuals.

Diseases of the Genital Organs.—*Retroflexion of the uterus,* especially in young unmarried women of visceroptotic habit and psychasthenic tendencies, frequently causes dyspeptic symptoms, such as intractable nausea and vomiting. These are also suggestive of *pregnancy. Acute salpingitis* and an *ovarian cyst with twisted pedicle* may produce nausea, vomiting, and epigastric pain as the result of marked reflex pylorospasm with gastric hypersecretion.

Diseases of the Central Nervous System.—Among the most important of the secondary functional gastric disturbances are those associated with various diseases of the central nervous system.

In the early stages of *progressive paralysis* ordinary dyspeptic symptoms often appear. In *tabes dorsalis* (locomotor ataxia) violent crises of epigastric pain (*gastric crises*) as well as intractable nausea and vomiting, sometimes with marked hypersecretion, come and go suddenly without apparent cause. These simulate cholelithiasis, renal calculus, intestinal obstruction, or perforating ulcer; sometimes there is intractable vomiting

with no pain. The attacks are often alarmingly intense and are separated by intervals in which the digestion is quite normal. Sometimes symptoms appear in the pre-ataxic stage. The Argyll-Robertson pupil, disturbance of gait, luetic history, and positive reaction of the blood or spinal fluid in the Wassermann test constitute the basis of diagnosis. Resection of the posterior roots of the spinal nerves has met with some success as a therapeutic measure. Similar crises occur very rarely in *general paralysis*, *multiple sclerosis*, *syringomyelia*, *pachymeningitis*, and *lesions of the posterior and lateral tracts*, as well as in morphinism.

Hysteria, Migraine, the Psychoses.—In *hysteria* practically any gastric syndrome may be produced by heterosuggestion or autosuggestion; the most frequent forms are *gastralgia*, *anorexia*, and *vomiting*. The anorexia may be so marked as to lead to noteworthy emaciation, and to justify forced feeding through the stomach-tube. *False anorexia* has also been observed; *i. e.*, the patient apparently eats nothing, but really consumes large quantities of food in secret. *Hyperorexia* and *oreximania*, an enormous increase in the appetite and food intake, are due apparently to fear of becoming thin. Some patients have *parorexia* (pica, malacia), which is a desire to eat non-edible substances such as chalk, dirt, and even fecal material (coprophagia). *Hysterical vomiting* is usually very violent and irregular. It occurs most often after meals. The very marked *distention of the stomach* sometimes seen in hysterical patients is usually caused by *aërophagia*.

The *treatment* of all these conditions is difficult: isolation, re-education, and suggestion are the most satisfactory therapeutic measures. Hypnosis has been employed.

The intractable nausea and vomiting associated with *migraine* are probably primarily neurogenic or psychogenic. Metabolic disturbances sometimes due to the overuse of sugars and starches or of animal proteins seem in certain cases to be predisposing factors. In the *psychoses* the digestive symptoms are usually purely imaginary; in *depressive states* anorexia, or fear of food, is a common symptom. An enormous increase of appetite is often associated with maniacal conditions.

Thomas R. Brown.

GASTRITIS

Acute Gastritis (*Acute Gastric Catarrh*).—With the exception of the type associated with the early stages of the acute infections, which is frequently more functional than structural, and that which follows the swallowing of corrosive substances, such as acids or caustic soda, acute gastritis is relatively rare. The more serious forms are not often recognized because the symptoms are submerged in the manifestations of the toxemia.

Etiology.—All irritant substances—mechanical, chemical, toxic, infectious—may cause inflammation of the gastric mucosa. Although functional disturbances of purely nervous origin may lower the resistance of the stomach, and thus render it more susceptible to the action of such substances, the cause is never strictly nervous. The primary or essential type

of gastritis results from dietary indiscretions, overeating, ingestion of bad or poorly masticated food, and individual susceptibility. Secondary or symptomatic acute gastritis is an accompaniment of organic diseases, such as acute local infections, exanthemata, typhoid, typhus, grippe, and general infections. In the latter, acute gastritis is caused by the specific bacteria and toxins, and secondary invading micro-organisms. Very severe infections are only occasionally associated with diffuse or localized *purulent gastritis*. *Toxic gastritis* follows ingestion of acids (carbolic acid is peculiarly popular among would-be suicides), caustic alkalies, various minerals (phosphorus, mercury, especially mercuric bichlorid), certain gases, poisonous mushrooms, and various medicines (iodin, etc.). The action of such substances may not only be direct, but also, as in the case of phosphorus and arsenic, take place when they are eliminated in part through the gastric mucosa. This is the reason for the necessity of repeated lavage in treatment.

Pathological Anatomy.—The degree of inflammation varies with the type of the causative agent. The lesion may be a slight superficial inflammation with hyperemia, edema, and some small round-cell infiltration, or very severe, and involve all the coats of the stomach wall. Superficial or deep ulceration or erosion, ecchymoses, hemorrhage from eroded vessels, or a diffuse oozing, certain lesions caused directly by the infection or toxemia, and others by the deleterious effect of infection on the blood-vessels of the stomach, such as infectious endarteritis, thrombi and emboli, are also seen. In *caustic* or *toxic* gastritis the lesions, as a rule, are most marked at the cardiac or pyloric orifices and lead subsequently to stenosis. There is often sloughing, and sometimes local or even general peritonitis. In the very rare *phlegmonous gastritis* diffuse or circumscribed abscesses form, usually below the mucosa, which sometimes involve the entire wall and occasionally lead to local or general peritonitis.

Symptoms and Diagnosis.—The symptoms in the *mild cases* may be very slight and are not characteristic. They may be those common to dyspepsia—fulness and discomfort after meals, nausea, dizziness, sometimes epigastric pain, and usually anorexia. In the severe cases these manifestations are more intense, and there is often increased thirst. The severe toxic condition may be evidenced by prostration, high fever at times, intractable nausea and vomiting, and agonizing epigastric pain. The tongue is usually coated, the breath heavy, the epigastrium tender to pressure and sometimes distended. Free hydrochloric acid may be entirely absent from the vomitus. Mild cases are very difficult to differentiate from purely functional disturbances, even when the etiology is considered. *Pain* may be very severe; it is caused by cardiospasm, pylorospasm, hyperperistalsis, and sometimes active antiperistalsis, and is accompanied by pallor, sweating, small rapid pulse, and an anxious expression. Such symptoms may, however, be caused not by severe acute gastritis, but by atypical *angina pectoris*.

The acute gastritis secondary to acute infection, as a rule, produces more striking gastric symptoms in the prodromal or early stages of the disease, although sometimes, as in severe typhoid fever or smallpox, the acute gastric symptoms may persist throughout the course of the disease. Rarely such symptoms predominate, as in certain severe general infections with black vomit and acute inflammation of the appendix or gall-bladder.

The symptoms of *toxic gastritis* are usually very severe. Violent nausea and vomiting, severe pain, and marked prostration occur, varying somewhat in character according to the type of causative agent (acid, alkali, mineral poison, poisonous gas, etc.). Acute gastric symptoms without *apparent* cause should always suggest toxicity, although, of course, in the vast majority of cases they are evidence of the onset of an acute infection. Sometimes when the patient is unconscious, or refuses to talk, a burn on the lip or mouth, or the odor of the breath, may be the only clue to the etiology, and may suggest the early and drastic therapy which is essential. The onset of such disturbances is usually very sudden and violent. Burning pain is felt in mouth, throat, and epigastrium; nausea and vomiting follow, the vomitus often being stained with blood. Sometimes hemorrhage, intense thirst, gastralgia, and the usual signs of collapse are seen; sometimes there is diarrhea, sometimes constipation, and occasionally complete anuria (bichlorid poisoning) which may lead rapidly to profound collapse, deep unconsciousness, and death. If the poison is less potent or present in smaller amounts, the symptoms are less striking, but slowly developing perforation with peritonitis may cause sudden aggravation of symptoms, or the relatively mild manifestations may gradually become more severe (mercurial poisoning). After the disappearance of the acute or subacute toxic symptoms, *complications* are likely to develop, such as stricture of the cardia or pylorus, perigastric adhesions, partial or complete atrophy of the gastric mucosa, or symptoms referable to the late effects of the poison on other organs (kidneys and intestines).

Phlegmonous gastritis, which is very rare both during the course of an infectious disease, and as an isolated condition which develops suddenly with no apparent cause, is manifested by a rapid evolution of all the signs of profound toxemia and, locally, by severe epigastric pain, vomiting, intense thirst, and usually diarrhea.

Prognosis.—If acute gastritis is not fatal, it may become chronic. The associated ulceration may produce cicatricial contraction of the stomach, pyloric obstruction, and perigastric adhesions.

Treatment.—In the *relatively mild cases* rest, local application of an ice-bag, or, in some cases, of heat to the abdomen, and a short period of starvation, followed by administration of mild liquids (albumin, diluted milk or beef juice), and then of soft, simple foods, is sufficient treatment if the case is seen early and the stomach emptied at once by gavage or emesis (apomorphin 0.005–0.01 hypodermically). An enema should be given to empty the bowels. Early starvation provides the best opportunity for a rapid cure. Later, prolonged elimination of irritating foods (mechanical, chemical, thermic) minimizes the possibility that acute gastritis may become subacute and chronic, for the stomach is peculiarly labile after these attacks and only by extreme care can recovery be made complete.

The starvation so necessary in the early stages is rendered easy by the lack of appetite and the distaste for solid food. The increased thirst can be satisfied at first with a few spoonfuls of water or cracked ice, and the necessary fluids supplied by rectal administration of water; often glucose ($2\frac{1}{2}$–5 per cent.) may be added, and soda (1–3 per cent.) or salt (1–2 per cent.). Such mixtures may be given by the Murphy drip method or as enemata (6–8 ounces every four to six hours). Later, sufficient water, especially alkaline water, may be taken by mouth. The simple cleansing

enemata which are at first the best means of opening the bowels may later be replaced by saline laxatives (phosphate of soda, milk of magnesia, the Bourget mixture). For the loss of appetite *following* the attack, nux vomica or other bitters should be given before meals, hydrochloric acid (10–20 minims) after meals. Bismuth subcarbonate in large doses (1–2 drams) or belladonna (3–10 minims of the tincture) often helps relieve the gastric discomfort, but if the proper treatment is started early, drugs are often unnecessary. In *infectious gastritis* the strictness of the regimen depends upon the severity of the infection. The treatment is a combination of that for gastritis and that for the infection.

The therapeutic measures employed for *toxic gastritis* vary with the nature of the poison and the quantity taken. Early emptying of the stomach by gastric lavage is practically essential, although the tube must be introduced with extreme care, especially when corrosive poisons have been swallowed. If the tube is not available or cannot be used, an emetic should be given (apomorphin hypodermically, hot salt water, ipecac, etc.). In certain cases when the poisons are re-secreted into the stomach (mercury, arsenic, gas poisoning) repeated gastric lavage is necessary. An antidote should be administered as quickly as possible, alkalies in large amounts (milk of magnesia, bicarbonate of soda, etc.) for acid poisoning; dilute citric or acetic acid to counteract caustic alkalies; sesquioxid of iron to prevent the action of arsenic; and milk or white of egg in mercury poisoning. After ingestion of mercury it is peculiarly important to wash out the stomach very frequently and to force fluids by mouth, by rectum, or subcutaneously, to the limit. These should often be combined with glucose which by its diuretic action lessens the chance of severe renal involvement. Administration of sodium thiosulphate (0.4–0.6 gram in 5 c.c. of normal salt solution every two days for four or five doses) has also been recommended for mercury and arsenic poisoning. Stimulation is usually necessary; caffein or camphor may be injected hypodermically, coffee or alcohol given by rectum; and if pain is severe, morphin, pantopon, or dionin hypodermically. Opium, often combined with belladonna, may be administered as a suppository.

The treatment of *phlegmonous gastritis* is that for severe gastritis, with surgical evacuation of localized pus. The severe diffuse type is almost inevitably fatal.

Chronic Gastritis (*Chronic Gastric Catarrh*).—The incidence of chronic gastritis varies according to one's definition of this disease. Usually the condition in which secretory or motor functional disturbances predominate, with slight if any modification of the gastric mucosa, cannot be considered chronic gastritis. Only when the symptoms seem to be evidence of persistent chronic inflammatory changes in the stomach should the term "chronic gastritis" be employed.

Etiology.—Any mechanical, bacterial, chemical, toxic, or thermic irritant, if of sufficient intensity and permitted to act for a long enough period, may cause chronic gastric catarrh. The susceptibility to such irritants varies markedly in different individuals. Some stomachs resist indefinitely serious dietetic indiscretions, persistent overeating, ingestion of food and drink which is too hot and too cold, alcohol and tobacco, improperly chewed food, etc. If the irritation is too severe, if it continues too long, or if the resistance of the stomach is lowered by inherent fragility or intercurrent causes, gastritis may develop. At times, the chronic type

develops from the acute, particularly when alcohol and toxins (especially the chemical poisons) are the etiological agents. There may, however, be no truly acute stage. *Primary chronic gastritis* gradually results from persistent ingestion of indigestible material, or of substances which are too cold or too hot, from careless habits of eating, improper mastication because of deficient or defective teeth, alcoholism, and the taking of irritating drugs (mercury, the iodids, cubebs, copaiba, etc.) for a long time, as well as from chronic infections of the tonsils and the accessory sinuses. Secretory anomalies develop first and lead to definite organic changes in the gastric mucosa. In *secondary chronic gastritis* the catarrhal inflammation is often secondary to other diseases of the stomach (ulcer, carcinoma, gastrectasy—possibly persistent gastric hypersecretion). It is also caused by chronic passive congestion or venous stasis (diseases of the heart, kidneys, or liver) or is associated with constitutional diseases (pernicious anemia, leukemia, nephritis, tuberculosis, carcinoma of other organs, gout, etc.).

Morbid Anatomy.—In addition to superficial catarrhal inflammation and hypersecretion of mucus there is, as a rule, involvement of the deeper structures—both interstitial and glandular. Small round-cell infiltration takes place, and there is a new growth of connective tissue with gradual destruction of the glandular apparatus. Probably an *early* glandular hypertrophy frequently precedes the later atrophy. In very advanced stages of the true atrophic form even the mucous glands disappear, and a marked flattening and aplasia of the gastric epithelium is noticeable. In many cases this stage is never reached. Erosion of the mucous membrane is sometimes seen and occasionally ulceration or hemorrhagic areas. The lesions are usually progressive, often beginning as an irritation with hypersecretion, and becoming finally subacid or achylic. In old or weak patients omission of the hyperacid phase is not uncommon; but in some individuals the hyperacid or irritative phase may persist for a surprising length of time. The achylic stage is occasionally never reached.

Symptoms may be almost entirely absent and are frequently not characteristic. They may differ little if at all from those of the banal dyspepsias, gastric atony, gastric neurosis, or early carcinoma. The appetite, especially for highly seasoned foods, is usually diminished, but occasionally increased. *Thirst* is sometimes marked; there is a bad taste in the mouth and epigastric fulness, discomfort, and a feeling of pressure after meals. Nausea is commonly associated with early morning vomiting of mucus in the advanced stages. Pyrosis, regurgitation of food, rarely pain, and loss of weight are manifestations in the later stages. Vomiting in the early stage can usually be traced to dietary indiscretions; later the vomitus consists of pure gastric mucus which is easily differentiated from pharyngeal mucus by its homogeneity and the absence of air. The bowels may be constipated, normal, or loose. Diarrhea is not uncommonly associated with achylia (gastrogenous diarrhea), and many of the chronic diarrheas in old people with defective or deficient teeth are gastrogenous. In nervous individuals, headache, vertigo, and depression are common symptoms.

There are few *physical signs* characteristic of chronic gastritis. The tongue is often coated, the breath heavy, the teeth defective or lacking, and the epigastrium sensitive to diffuse and, rarely, to local pressure. The loss of weight which is obvious in the late stages is caused, possibly, by loss of appetite and partly by fear of the discomfort produced by eating. Sec-

ondary anemia sometimes develops. Some patients have only intestinal symptoms, *i. e.*, the gastrogenous diarrhea secondary to achylic gastritis, extremely rapid emptying of the stomach, often without increased peristalsis, but with an open pylorus. In hyperacid gastritis, however, hyperperistalsis is not uncommon. Hypermotility is usually the rule.

Diagnosis is often difficult, and in the early stages impossible. A complete history, especially of the etiological factors and a knowledge of the changes in the gastric contents, sometimes permit recognition of acute gastritis. Persistent abuse of food and drink, alcoholism, an alcoholic tremor, especially of the tongue, poor teeth, large quantities of gastric mucus in the stomach after a test-meal or fasting, and possibly an increase in the number of pus or epithelial cells in hyperchlorhydria are of diagnostic importance. Usually these are seen in the relatively late stages of hypochlorhydria, achlorhydria, or achylia, but they are occasionally present in the relatively early stages. Signs and symptoms of other organic diseases of the stomach, especially ulcer or neoplasm, are absent.

Prognosis.—The clinical manifestations of relatively early cases usually disappear, but morphological lesions always remain. Patients with advanced disease can, as a rule, be made much more comfortable by treatment, but never cured. Administration of the proper diet and hydrochloric acid therapy often relieves achylia and diarrhea remarkably.

Prophylaxis.—Suitable habits of eating, the choice of correct foods, the partial avoidance of notoriously irritating foods and drinks, and proper oral hygiene prevent chronic gastric catarrh.

Treatment.—After the condition has become established the irritating substances must first be entirely eliminated. The mouth must then be put in good condition and suitably cared for; focal infections should be removed and adequate false teeth provided to replace those removed. Dietary treatment is essential. At first only very simple foods, milk, milk and lime-water or Vichy, soft cereal gruels, buttermilk, or *Bacillus acidophilus* milk (especially when there is a deficiency of hydrochloric acid) should be administered, but later the diet may consist of soft, non-irritating substances. Milk and cereals and purée of green vegetables should constitute the food supply for a long time. The elimination of meat for quite a while is desirable. When taken, only those of the finer variety, fish, the white meat of chicken or a lamb chop, should be permitted. Fried and greasy foods, very hot or very cold substances, pastry, strong condiments, the coarser meats and vegetables, stimulants (alcohol, coffee—if possible), and tobacco are to be forbidden. It is, however, essential that a sufficient number of calories be taken. For patients with hyperchlorhydria, cream, fresh butter, and olive oil are particularly useful; for those with subacidity or achylia, beef juice, bouillon, and acid fruit juices are advisable. Frequently five or six small meals at even intervals are better than three large meals.

When the gastritis is severe a short course of gastric lavage morning and night, preferably with warm alkaline waters (bicarbonate of soda—1 or 2 drams to the quart), is very helpful, but such therapy should be continued only a relatively short time before it is replaced by the administration about half an hour before meals of a cup of hot water alone, mixed with a pinch of soda, or, in the subacid cases, with ordinary salt. Except for acute gastritis, pyloric stenosis with retention, and certain postoperative

conditions, chronic gastritis is practically the only condition which necessitates lavage. This treatment should not be continued after the patient really begins to improve. For constipation, phosphate of soda, Carlsbad salts, or the Bourget mixture may be added to the cup of water in the morning. If the appetite is poor, bitters such as nux vomica or gentian may be employed, often with hydrochloric acid and pepsin in the subacid conditions. Marked fermentation, especially in the gastritis secondary to organic disease (carcinoma, pyloric obstruction), may be treated with resorcin, salol, magnesium salicylate, or perhydrol in 5-grain doses.

In addition to these measures every effort should be made to build up the patient. The proper amount of fresh air, exercise, and rest, may, with the patient's co-operation, result in great improvement and sometimes in clinical cure. The diet must be carefully regulated for an indefinite period if permanent improvement is to be expected. It is wise in a general way to vary the treatment according to the quantity of hydrochloric acid secreted, both from the medicinal and dietetic point of view. Achylia, especially with diarrhea, requires administration of relatively small doses of hydrochloric acid (10 drops of the dilute acid before, 15 drops after meals). The diarrhea, which sometimes persists for months, stops almost immediately under such medication. The acid therapy must, however, be continued indefinitely. In rare instances ingestion of pancreatin several hours after meals helps this acid treatment. As a rule alkalies, especially sodium bicarbonate, are very useful: they should be given before meals when the acidity of the stomach is diminished, after meals when it is increased. Milk of magnesia or calcined magnesia, sometimes with belladonna, is of value when constipation is marked.

THOMAS R. BROWN.

DISPLACEMENT OF THE STOMACH

(*Gastroptosis*)

Gastroptosis, or falling of the stomach, is by far the most common type of displacement, and practically the only one of clinical interest. In rare instances the stomach becomes inverted, or is laterally or vertically displaced by abdominal tumors, ovarian cysts, the pregnant uterus, or marked retraction of the left lung. Diaphragmatic hernia produces an extremely rare but interesting upward displacement which is manifested by symptoms not unlike those of gastric ulcer with obstruction. Practically, however, only gastroptosis need be considered.

The term should be applied only to conditions in which the stomach in the upright position extends below the iliac crests. There is often a drawing out but rarely true ptosis of the cardia. Although the pylorus is more or less ptosed it is often held surprisingly high, so that the stomach assumes a hammock appearance. The ptosis *per se* does not cause symptoms, but the associated difficulty in emptying, which is partly produced by inherent or congenital atony of the gastric musculature and partly by the drag of the ptosed viscus on the relatively fixed duodenum, may subsequently lead to

true organic stenosis and gastrectasis. Gastroptosis is almost always associated with downward displacement of other viscera, such as the right kidney and the hepatic flexure of the colon, and often in women with retroversion or retroflexion of the uterus. Occasionally cardioptosis is seen. In other words, gastroptosis is only one manifestation of splanchnoptosis or Glénard's disease.

Etiology.—The condition is seen in about 20 to 30 per cent. of all women and in less than 5 per cent. of men. It is almost always congenital and associated with a characteristic formation of the body—long narrow thorax, narrow costal angle, vertical ribs, contracted hypochondrium, and floating tenth ribs (Stiller's sign). While most ptosis is primarily congenital, it may be wholly or in part acquired. Persistent overloading of the stomach, or overingestion of fluids, repeated pregnancies, especially with poor after-care, various diseases associated with rapid loss of weight, and the wearing of high, tight corsets may be causes. According to Keith, the disease is evidence of overbalancing by the inspiratory muscles of the abdominal muscles and ligamentous supports of the abdominal viscera. In a certain sense splanchnoptosis is the penalty for upright posture.

Symptoms and Diagnosis.—It must be kept in mind that ptosis is not the cause of symptoms, but predisposes to atony and delayed emptying of the stomach. The symptoms are, in reality, those of gastric atony, with, in some cases, additional manifestations caused by pyloric stenosis. Consequently, they include a sensation of fulness after eating or drinking, early satiation, gaseous eructations, usually constipation, lack of appetite, and frequently various evidences of nervous indigestion, such as headache and depression. The congenital bodily fragility is usually accompanied by inherited psychic instability. Consequently atonic dyspepsia and psychasthenia are present in the majority of cases.

Fulness of the lower half of the abdomen and retraction of the upper half when the patient is standing; succussion splash or clapotage of the stomach; the relief of symptoms in the prone position or when the abdomen is supported by the hands or by a mechanical support (Glénard's belt test); and the characteristic body form indicate the correct diagnosis. This can be easily confirmed by distention of the stomach through a stomach-tube, by giving bicarbonate of soda and tartaric acid, and by *x*-ray examination. In *x*-ray plates the stomach appears below the iliac crest and most of the barium is in the dependent portion; sluggish peristalsis, delayed motility, sometimes cardiospasm, and sometimes the "hour-glass stomach" are also evident. The fluoroscope demonstrates how much better the stomach functions in the prone than in the upright position. The costal angle is narrow, the general, but especially the abdominal, musculature is usually flabby, the patient is often thin, and the abdominal aorta pulsates markedly and is easily palpable. Atony of the viscus is frequently strikingly evidenced by the relative lack of discomfort which follows artificial distention. Unless the disease is far advanced and true pyloric obstruction has resulted from persistent traction on the pylorus and duodenum by the overloaded stomach, the fasting stomach test (twelve hours after the rice meal) is usually normal. Six hours after ingestion, however, rice is usually present and the acid content may be increased or normal. Most frequently there is subacidity, and achlorhydria or achylia in the more marked cases. The eructation and gastric distention are partly caused by aëro-

phagia. Digestion is slow, discomfort comes soon after eating and largely depends upon the quantity of food taken. Drowsiness often follows meals. Rest in the prone position after meals usually gives great relief. Sudden pressure upon the abdomen frequently causes pupillary dilatation, which is presumably due to the instability of the vegetative nervous system. As a rule, symptoms develop slowly, and to hope for much relief they must be recognized early.

Treatment.—Early employment of prophylactic and therapeutic measures may give brilliant results, while in the later stages the effects of treatment are often very disappointing. It is important to realize that falling of the stomach leads to gastric atony, and that it is consequently essential to recognize the type of body in which this characteristically takes place. This is necessary in order that the tone of the abdominal musculature may be improved, the hypochondriac spaces enlarged, overloading of the stomach avoided, the quantity of intra-abdominal fat increased as a support, the diet made fattening and nutritious, and excess ingestion of fluid with meals avoided. Deep breathing, abdominal and general exercises should be taken, outdoor sports, and at times abdominal massage and general hygienic measures instituted for prophylaxis.

Symptoms of chronic dyspepsia are usually, however, fully developed when the patient is first seen. Treatment should consist of more intensive employment of the prophylactic measures, with elevation of the foot of the bed (6, 9, 12 inches or more), rest after meals if possible, the wearing of a well-made support for the lower abdomen (corset, binder, adhesive plaster bandage) which is applied in the morning before rising, abdominal massage which may often be given successfully by the patient with a $2\frac{1}{2}$ or 5 pound cannon ball, proper regulation of the diet, tonic treatment, and employment of general hygienic measures. In mild cases, the quantity of fluid taken with meals should be reduced to not more than one glass or half a glass. The food ought to be nutritious, not too coarse, and concentrated. If possible, intermediate feeding of milk, milk and cream, and raw eggs is desirable in that it strengthens and also fattens the patient. Sometimes five or six small meals, at other times two or three large meals are most easily taken. When a thorough course of rest and upbuilding is necessary, little or nothing should be given by mouth for the first two or three days. Glucose, soda, and salt and water may be administered by rectum during this period. Thereafter the oral food intake may be increased, until finally the patient is able to take three large meals, 1 or 2 quarts of milk, and 6 to 12 eggs daily. Marked increase in weight and strength should result. Massage is very helpful for severe conditions, particularly in combating constipation. Optimistic psychotherapy is invaluable for correction of the psychasthenia so frequently associated with marked gastroptosis and atony. Rest in the prone position after meals often gives relief. In a modified form, the essentials of this treatment must be continued for a very long time, often for months, if the optimum benefit is to be obtained. If the patient understands the reasons for the treatment and is willing to co-operate, the results may be brilliant.

Cacodylate of iron or sodium may be given hypodermically, and bitters, orally, to stimulate the appetite. Strychnin in large doses is a very useful drug. When re-education and establishment of proper habits with normal stimuli fail to relieve constipation, instillation of cotton-seed oil or olive

oil (2–4 ounces by rectum at night to be retained all night), or the simple laxatives such as cascara, senna, or phenolphthalein may be employed. Mineral oil is often too bulky and not well borne.

If all other measures fail after long, persistent, and repeated trial; if the patient is drifting into a state of chronic gastro-intestinal invalidism, and the stomach shows considerable dilatation and evidences of contraction of the pylorus, surgical intervention may be justified. Such therapy has, however, proved singularly unsuccessful, except in cases of well-marked pyloric obstruction caused by continuous traction of the overloaded, atonic viscus.

Pyloroplasty has given some good results; gastro-enterostomy is probably less successful; and gastropexy and other forms of fixation (hammock operation, suture of stomach to anterior abdominal wall, etc.), which are said to be helpful in certain cases, seem to leave the patient in a condition worse than that preceding operation. There is considerable danger in fixing any organ which, physiologically, is relatively mobile.

Thomas R. Brown.

PEPTIC ULCER

(Gastric and Duodenal Ulcer, Round Ulcer, Simple Ulcer)

Peptic ulcer was first clearly described by Cruveillier in 1829. The incidence varies markedly in different countries, being recorded as 0.8 per cent. in Russia, 1.3 per cent. in North America, 5 per cent. in England and Germany, and 16.7 per cent. in Denmark. The condition is less prevalent in beer-drinking Southern Germany than in "Schnapps"-drinking Northern Germany; and there is considerable evidence that it is less frequent among vegetarians than among those who eat much meat. Peptic ulcers probably develop far more often than they are clinically recognized (0.5-1 per cent. of patients). Occupation seems to play no etiological rôle, and heredity little or no part in their causation. Statistics apparently show that they are seen two or three times more often in men than in women. Acute gastric ulcers, however, certainly develop as frequently, if not more frequently, in women between twenty and thirty years of age than in men. The chronic duodenal ulcer, on the other hand, appears most often in men between the ages of thirty and fifty. Ulcers are seen in people of all ages, in infants a few days old, and in the very aged. The incidence is highest, however, in women between twenty and thirty and in men between thirty and fifty. The lesion is very rare in individuals less than twenty years of age. In Moynihan's Clinic, out of 718 cases operated upon, 531 were duodenal (433 men, 98 women), 164 were gastric (83 men, 81 women), while in 22 (10 men, 12 women) gastric and duodenal ulcers were both present.

Peptic ulcers may be acute or chronic. The acute type is either simple or spreading, and the chronic practically always develops from an unhealed acute ulcer. The round or peptic ulcer of the stomach is much more clean-cut than the ulcers which appear as transitory erosions or terminal lesions

during the course of many of the infectious diseases such as influenza, measles, and smallpox, and in cardiovascular diseases, nephritis, acute and chronic gastritis, carcinoma of the stomach, acute endocarditis, cirrhosis of the liver, etc.

Fully two-thirds of gastric ulcers are situated in that portion of the stomach where the mucous membrane is not devoted to the elaboration and secretion of hydrochloric acid, and where the circulatory, muscular, and nervous activity seems to be greatest. Very few occur in the area chiefly devoted to receiving food and secreting acid and pepsinogen.

Etiology.—Two conditions are essential to the development of a peptic ulcer: a lesion of the mucous membrane (abscess, necrosis, hemorrhage); and digestion of the pathological portion of the stomach wall which has become a *locus minoris resistentiæ*. Evidence of the importance of this second factor is to be found in the fact that peptic ulcers develop only in portions of the mucous membrane which are bathed in acid gastric juice—in the stomach and in the first and sometimes the second portion of the duodenum. They occur also at the cardiac end of the esophagus and in the contiguous jejunum after gastro-enterostomy.

The belief that *trauma* plays a noteworthy etiological rôle is highly improbable because few of the individuals who subject their stomachs to trauma or to mechanical, chemical, and thermic irritation suffer from peptic ulcer: and ulcers produced experimentally in animals by trauma practically always heal rapidly.

Infection has always been supposed to be of etiological importance, and Rosenow has recently produced both acute and chronic ulcer by intravenous injection of streptococci obtained from lesions in the throat and mouth. These ulcers have contained micro-organisms morphologically and culturally similar to those injected. Probably, however, infection is, for the most part, not a primary but a secondary cause.

Disturbance of the blood-supply of the area involved is of primary importance, and may be due to various conditions, the formation of thrombi and septic emboli; development of small aneurysms or reduction in the size of the blood-vessels (arteriosclerosis); persistent spasm of the vessels with resultant local ischemia of reflex nature; disturbances of the gastric nerve supply; or traction upon the pylorus or duodenum in marked gastroptosis.

The caustive rôle of the *nervous system* is being more and more emphasized. In animals, experimental injury of the celiac axis or of the splanchnics supplying the stomach is known to produce ulcerative lesions exactly analogous to ulcers in man. Usually, however, not organic disease but a functional disturbance of the nerves supplying the stomach causes ulcer. Lack of balance between vagus and sympathetic, and functional irregularities of the trophic nerves of the stomach are apparently purely psychogenic, although many observers insist that congenital influences and toxemia, possibly of intestinal origin, play a considerable rôle. Careful observation seems to corroborate the idea that peptic ulcer is not a local but a constitutional disease, and that in its origin and in the recurrence of symptoms psychic factors are important. Perhaps the high incidence of ulcers in Germany and Russia since the World War is caused far more by wide-spread depression, fatigue, worry, and lowered resistance than by coarse, comparatively indigestible, and mechanically irritating food. It is hard to believe that the effects of alcohol, condiments, and very hot or

cold food are etiologically fundamental. Gray believes that tobacco causes ulcer by paralyzing the sympathetic ganglion-cells. Lack of antiferments may favor ulceration; and some observers insist that the lesions are commonly associated with a certain type of body form—the orthotonic.

Of the several possible primary causes, the vascular and neurogenic are the most probable. Hyperacidity and hypersecretion are the effects and not the causes of gastric ulcer; and irritating foods and drinks, pathogenic bacteria, and motor disturbances due to pylorospasm prevent rapid and successful healing. All these primary, secondary, and accessory factors must be kept in mind if therapy is to be successful and the chance of recurrence minimized.

Morbid Anatomy.—The ulcer is usually single, but is said to be multiple in between 20 and 30 per cent. of cases coming to operation. As many as 20 have been found in one patient. *Gastric ulcers* are usually situated in the neighborhood of the pylorus, probably most often at the lesser curvature, and less frequently in the posterior and anterior walls. "The pyloric vein or veins and the pyloric white line indicate with quite sufficient clearness the separation between the stomach and the duodenum. A *duodenal ulcer* is almost always ½ inch or more from these landmarks, though it may extend up to them, or even beyond them into the stomach. A gastric ulcer is very rarely within 1½ inches of the pylorus; it is, with the fewest exceptions 2 inches or more from the pylorus. A pyloric ulcer, an ulcer beginning exactly at the pylorus, is excessively rare. Pyloric stenosis is virtually always duodenal stenosis" (Moynihan).

Ulcers are concentric, round, oval, or irregular, and vary in size from that of a pin-point to that of a silver dollar or even more. They may be very superficial, as in the case of the simple erosion. They may penetrate the mucous membrane alone, or they may involve the muscularis mucosa, the musculature, and the peritoneum, and even lead to local or general peritonitis by penetrating the peritoneal coat. Perigastric adhesions and a walled-off or subphrenic abscess may develop; the stomach may become adherent to the liver, gall-bladder, pancreas, spleen or intestine, and occasionally the lesion may perforate into the intestine (gastrocolic fistula, duodenocolic fistula). As a rule the limits of the ulcer are definitely defined and the lesion often presents a punched-out appearance. In certain cases, however, especially in old recurrent ulcers, the limits may be ill-defined. Chronic ulcers with much callosity are often associated with a hard palpable tumor extremely suggestive of a scirrhus. There is always loss of substance, necrosis, small-cell infiltration, hyperemia, and formation of new connective tissue which produces scars. Callouses and cicatrization occasionally lead to marked deformity (hour-glass stomach, multilocular stomach, etc.). The local lymphatic glands are often enlarged, palpable, and show evidence of recent or old inflammation, especially when the ulcers are deep. About the ulcer there may be definite gastritis of the atrophic or glandular hyperplastic type; the latter may possibly lead to malignant degeneration in about 5 per cent. of cases.

Symptoms.—The patient with gastric or duodenal ulcer nearly always gives a history of chronic gastric disturbance, usually of some years' duration, during which there have been remissions, often with complete absence of symptoms. The periodic character of the attacks is a striking feature of the disease; the symptoms are rarely continuous. In certain cases there

are no symptoms at all until signs of perforation appear or severe hemorrhage takes place. Moynihan states that "the chief clinical symptoms of ulcer are pain, vomiting, and hematemesis, and of these the really important one is pain. The extremely significant feature with regard to the pain is its punctuality. In the same patient, after the same meals it appears with the most exact regularity after the same intervals of comfort. In cases of *gastric ulcer* the pain, which after an interval follows the taking of a meal, gradually disappears before the next meal. In cases of *duodenal ulcer* the pain continues until the next meal or until food is taken to give ease to the wearisome pain. The rhythm of gastric ulcer is food, comfort, pain, comfort—of duodenal ulcer, food, comfort, pain—a quadruple rhythm in the former disease, a triple in the latter." Although in a few cases the pain is due to neuralgia or neuritis of the peritoneal nerves, particularly when the ulcer is deep and associated with adhesions, it is usually caused by pylorospasm. This reflex disturbance may result from many extragastric causes, such as renal or ureteral calculus, appendicitis, pyosalpinx, ovarian cysts with twisted pedicle, peritoneal adhesions, marked gastroptosis when the duodenum is high and fixed, and even from intractable constipation with marked cecal stasis.

The character of the pain and the time of occurrence vary with the location and nature of the lesion. That which develops shortly after a meal is probably caused by ulceration of the lesser curvature; that delayed for thirty minutes to two hours after eating, by pyloric ulcer; and the so-called hunger pain, which is not felt for two to four hours after ingestion of food, by duodenal ulcer. Since reflex pylorospasm is less frequently associated with ulceration of the anterior and posterior surfaces and of the greater curvature, ulcers in these regions are frequently painless, and may pass unnoticed. The depth of the lesion also affects the quality of the pain; and adhesions, involvement of contiguous organs, and the receptivity of the subject are not without influence. That hypersecretion of hydrochloric acid occasions pain is highly improbable, for pain may be severe when the acid secretion is diminished, and vice versa. The relief which follows ingestion of food and soda is, in all probability, due to relaxation of the pylorospasm which facilitates emptying of the stomach. Coarse and highly seasoned foods usually increase the discomfort; bland foods are innocuous.

The pain is usually located behind the xiphoid or in the epigastrium; on the right side in duodenal ulcer, on the left, in gastric ulcer; and, in between 25 to 30 per cent. of patients, is also felt in corresponding dorsal points and rarely in the shoulder. Change of position may affect it markedly. Cutaneous hyperesthesia in the epigastric region is fairly common. In character, the pain is sometimes agonizing, but more often dull and merely a sensation of burning or discomfort. Any change in the quality, punctuality, and periodicity is always suggestive of complications, such as perigastric or periduodenal adhesions, or cicatricial, pyloric, or duodenal stenosis.

Vomiting usually occurs when the pain is most severe. It is frequently preceded by nausea, is often induced by the patient, and may give great relief. This symptom is seen in less than 50 per cent. of patients with ulcer, and is usually not associated with the uncomplicated duodenal type. In very neurotic or hysterical individuals it may be so persistent as to necessitate feeding through a duodenal tube. Marked organic stenosis of the

pylorus produces very severe vomiting, which may, by demonstrating the length of time food is held in the stomach, indicate in some measure the extent of obstruction. The vomitus, which is often very acid, may consist of practically pure gastric juice containing 0.4 to 0.5 per cent. acid.

While *bleeding* is very common, hematemesis occurs in hardly more than 10 per cent. of all cases. Melena indicates extensive bleeding in about 25 per cent. of patients. In individuals who have a history of ulcer or indefinite digestive disturbances, sudden collapse with anemia should always suggest hemorrhage from a duodenal ulcer. The feces should be carefully watched, for a large tarry stool confirms this suspicion. Large quantities of blood are sometimes lost, but the hemorrhages are rarely fatal *per se*. The blood may be bright red, or, if the hemorrhage is not severe, give a coffee-ground or black appearance to the highly acid gastric juice. The percentage of hemoglobin may fall to 40, 30, or even less. The symptoms characteristic of the rapid loss of a large amount of blood appear, and immediately preceding hemorrhage the epigastric pain and discomfort increase.

The *appetite* is usually normal, but may be increased. Frequently the patient reduces the food intake markedly because of fear of the effect of ingested material (sitophobia). Lack of appetite is not suggestive of duodenal ulcer; it is sometimes marked in very old people. Except when pyloric obstruction causes severe vomiting the *nutrition* remains unchanged. In duodenal ulcer true bulimia is sometimes seen. The usual dyspeptic symptoms, *pyrosis, belching*, and *fulness and discomfort after meals*, may or may not be present and are not characteristic. In certain cases, however, they may be the only symptoms.

Of the *objective manifestations*, the most important are tenderness on pressure of the epigastrium, changes in the gastric contents (fasting and after the test-meal), the conditions revealed by *x*-ray, and the character of the stools. *Tenderness on pressure* in the epigastrium is a very common symptom which is sometimes associated with cutaneous hyperesthesia and pain in the back. The muscular resistance (*défense musculaire*) is often increased. With perforation and local peritonitis the pressure pain may be exquisite, and the epigastrium board-like.

The *gastric contents* after the test-meal varies markedly. Probably hyperacidity is usual at the beginning unless previous disease such as gastritis or various extragastric diseases, usually associated with lessened gastric acidity, has inhibited the glandular activity of the stomach. In practice, however, the condition is rarely seen at the onset and somewhat less than 50 per cent. of patients show high normal or hyperacid conditions. In rather more than 50 per cent. of cases the figures are well within normal limits; occasionally subacidity occurs and rarely anacidity. Hyperacidity is more common in duodenal than in gastric ulcer. Persistent hypersecretion, which is usual in benign pyloric obstruction, quite frequently accompanies duodenal and less frequently gastric ulceration. During fasting there is often hypersecretion in cases of duodenal ulcer, and this is associated with gross retention of food when there is pyloric or duodenal organic obstruction. Even with purely functional pylorospasm, slight microscopical retention of food (rice for twelve hours) is not unusual. It is interesting that the acid content is often quite as high after a successful cure as during the period of active symptoms. Persistent hyperacidity after the test-meal or during fasting is unquestionably a sign of value in the diagnosis of ulcer;

absence of this condition, however, by no means precludes the possibility of ulcer.

x-Ray plates may be extremely valuable when properly taken and interpreted, but should never be depended upon to the exclusion of other factors. They should be taken with the patient in different positions, and repeated after an interval when he has received atropin, if the possibility of spasm is to be ruled out. Both *direct* and *indirect* changes are important. Delayed motility, pyloric spasm in gastric ulcer, hyperperistalsis, early hyperirritability with a later delay (paradoxical hypermotility) in duodenal ulcer, are significant manifestations, although they may occur without ulceration. The *direct* findings, to which more and more attention is being paid, are a persistent filling defect, the presence of a niche, a permanent irregularity, or a penetrating cavity (perforating ulcer). The latter not only is evidence of ulceration, but an indication of the location, extent, and depth of the lesion. Fluoroscopic studies should be made with the patient erect, prone, and on the side. The abdomen should be palpated during the examination to determine any possible correlation between the filling defect or irregularity and the local tenderness. An hour-glass disfiguration of the stomach is sometimes due to ulceration with cicatrization or spasm in the zone of the lesion, but may be of purely functional origin, as in the visceroptosis of highly sensitive individuals. The functional type may disappear after administration of belladonna and bromids. Perigastric adhesions may cause the stomach to assume a multilocular shape.

The presence of *occult blood* in the stool when the diet is free from meat and there is no bleeding in the rectum, mouth, or pharynx is extremely significant. Blood is usually derived from small thrombosed vessels or newly eroded capillaries. Bleeding often results from the irritation of food. The disappearance of blood from the feces suggests healing. The benzidin test (dry method) satisfactorily demonstrates the presence or absence of blood in the stools.

Atypical Symptoms.—Frequently, atypical symptoms predominate or are superposed on those characteristic of ulcer. Rodari mentions the following types: (1) Pain which is independent of the ingestion of food, often very severe, and usually regarded as nervous gastralgia; (2) absence of pain except for the vague, indefinite digestive discomfort usually associated with nervous indigestion; and (3) a typical syndrome of which chronic gastritis, a fickle appetite, epigastric discomfort, fulness and feeling of pressure after meals, and occasional vomiting of food or mucus are the most striking features. Careful gastric analyses, examination of the stools for occult blood, and *x*-ray studies are invaluable for the diagnosis of such conditions. Very rarely *duodenal ulcer* may cause *icterus*. If this symptom is predominant the condition is usually mistaken for *catarrhal jaundice*. Deformities of the duodenum following cicatrization of an ulcer may produce stenosis of the common duct.

Diagnosis.—In a large proportion of cases duodenal ulcer, and, in a much smaller proportion, gastric ulcer can be diagnosed with almost absolute certainty. The periodicity of the attacks, especially when the ulcer is duodenal, the punctuality of the pain, the exacerbation of symptoms by ingestion of coarse and highly seasoned food, their mitigation and often temporary disappearance following restriction to a soft, bland diet, the presence of occult blood in the feces, pain on pressure over the duodenum

or stomach, hyperacidity or hypersecretion, and the characteristic changes in the *x*-ray shadow all make great certainty of diagnosis possible. A small percentage of duodenal ulcers, and a larger percentage of the gastric type, produce symptoms which are very confusing, atypical, and not in the least suggestive of ulceration. In such cases many characteristic signs are also lacking and every possible method of diagnosis must be utilized if the condition is to be recognized. Psychogenic or reflex pylorospasm, because it causes discomfort after meals which is relieved by alkalies, and irritability of the stomach with pylorospasm, as revealed by *x*-ray examination, are often incorrectly diagnosed as ulcer. In order to prevent such mistakes it is essential to remember that the symptoms typical of ulcer may be found in diseases of the appendix, gall-bladder, kidney, or ureter, and that, in a certain proportion of patients, the symptoms are too vague to suggest ulceration until perforation, hemorrhage, or operation for some other disease reveals the nature of the lesion. Consequently, a thorough *x*-ray examination is desirable whenever disturbances without apparent cause occur, especially in early middle life, for it may provide definite evidence of organic disease, ulcer, or cancer, when the history has in no way warranted such diagnosis. Because purely functional spasm may be persistent, it is desirable to repeat such examinations several times before diagnosis is considered final. A tentative diagnosis of ulcer, particularly of duodenal ulcer, can be based upon the punctuality and periodicity of symptoms. Some patients, however, have pain only after certain meals or at certain times of the day (between 1 and 2 A. M.). The disappearance of occult blood in the stools when the diet is bland is also suggestive of ulcer; if persistently present, bleeding may be due to carcinoma or occasionally to a very deep chronic ulcer of long standing. In the gastric contents, on the other hand, occult blood is of little significance, because the hemorrhage usually results from trauma by the stomach-tube.

In the *differential diagnosis* diseases of the gall-bladder and urinary apparatus, nervous indigestion, various intestinal lesions, such as appendicitis, adhesions and intestinal parasites, carcinoma, pancreatitis, gastroptosis, epigastric hernia, and perhaps even conditions associated with marked chronic constipation may cause confusion.

In cholecystitis, cholelithiasis, renal or ureteral calculus, and pyelitis, and to a much less extent in nephroptosis with dilatation of the renal pelvis, the lack of a close relationship of symptoms to the ingestion and character of food, the absence of occult blood in the stools, and the absence of a persistent, irregular filling defect or niche during *x*-ray examination, as well as the presence of pus or blood in urine obtained by catheter when there is renal infection or stone, should be adequate for diagnosis. A persistent, localized, reflex spasm in the stomach or duodenum may sometimes, however, make differential diagnosis by *x*-ray very difficult. Chronic lesions of the gall-bladder tend to cause subacidity or achylia, and may sometimes be recognized from an old history of icterus or the passage of acholic stools. Appendicitis in certain instances produces *only* epigastric symptoms, and if associated with reflex pylorospasm and hypersecretion may prove a difficult diagnostic problem and lead to operation for gastric or duodenal ulcer. Some ulcers are so small that they are overlooked, and others so superficial as to render palpation or inspection useless as methods of diagnosis. In the gastric neuroses, the obvious psychic instability, the lack of

punctuality and periodicity in the development of symptoms, and the fact that the most indigestible foods can often be eaten with impunity while the simplest cause violent symptoms, are pathognomonic. Adhesions, especially between the gall-bladder and stomach or duodenum, often produce a syndrome almost identical with that of ulcer and may persistently distort the *x*-ray shadows. The evidence of eosinophilia in the blood and of ova or parasites in the feces may reveal the parasitic character of the most puzzling of ulcer-like conditions. Sometimes it is very difficult to differentiate chronic ulcer and carcinoma, although ordinarily persistence of bleeding, low or absent gastric acidity, loss of appetite, and marked asthenia should certainly suggest malignant disease. The gastric crises of tabes should always be suspected. Whenever the patient has had syphilis or shows evidence of the disease, such as the Argyll Robertson pupil and ataxic gait, the possibility of a gastric crisis should be kept in mind. A small epigastric hernia should always be looked for; if the omentum is adherent, the symptoms may almost exactly simulate those of ulcer, just as they do in high-grade gastroptosis with atony and tension on the relatively fixed duodenum.

Complications.—The most serious complication is *perforation*. This may be the first definite evidence of ulceration and may occur in the acute or chronic stage of ulceration. According to Dillon, it is seen in about 5 per cent. of the duodenal cases, and in somewhat less than 2 per cent. of the gastric cases. It may lead to *general peritonitis*, which, when there is hyperacidity, may at first be due more to chemical than to bacterial action. Inability to urinate often results from irritation of the pelvic peritoneum by the fluid from the perforation. The peritonitis may be localized and lead to the formation of abscesses or to extensive perigastric adhesions, or both. The onset, which is usually very sudden, the agonizing pain, and the symptoms of shock, as well as the history of ulcer, usually suffice for diagnosis. Without the history of ulcer it is often very difficult to differentiate the picture from that of hemorrhagic pancreatitis or high intestinal obstruction. The perforation is usually, although not always, small, often only the size of a pin-point. The success of operation, which is the only safe form of treatment, varies indirectly with the interval between perforation and operation. In certain cases the condition remains localized because of adhesions to the liver, spleen, pancreas, intestine, or even abdominal wall. The latter condition may permit formation of a gastro-intestinal or gastrocutaneous fistula.

Hemorrhage, which may also be the first symptom, is almost as serious as perforation. Although a large quantity of blood may be lost, this complication is in itself rarely fatal, especially since blood transfusion has become so easily available. Immediate surgical treatment is rarely, if ever, necessary, but may be employed to cure the ulcer itself after the patient has regained strength.

Carcinomatous degeneration of an ulcer occurs, according to most clinicians, relatively infrequently,—in not more than 5 to 10 per cent. of gastric ulcers, practically *never* in duodenal ulcers. Loss of appetite, decreasing acidity, persistent presence of occult blood in the feces, however simple the diet, and usually loss of weight and strength—symptoms which are, as a rule, unusual in ulcer—should suggest the true diagnosis. Exploratory operation should follow even a suspicion of this complication.

Perigastric adhesions with deformity of the stomach (hour-glass or multilocular deformation, etc.), *pyloric stenosis* due to cicatrization and contraction of the ulcer, and *callous formation*, are all relatively common complications. It is well to remember that when the clean-cut syndrome of ulcer begins to be blurred and the symptoms tend to be constant or irregular, with increasing difficulty of evacuation, complications are generally developing. Surgery is then the only useful form of therapy.

Treatment.—Until the primary factor in the etiology of ulcer is ascertained, prevention cannot be entirely successful. The establishment of proper habits of eating, the avoidance of notoriously irritating (chemical, mechanical, thermic) articles of food, the minimization of worry, strain, and hurry—at least at meal times—the removal of infection from teeth, tonsils, and accessory sinuses, the prevention of chronic constipation by regulation of diet and exercise, and the surgical removal of disease elsewhere in the abdomen are, however, measures which tend to lower the incidence of ulcer. These are essential features in the treatment of ulcer whether surgery be employed or not. If cure is to be complete, such therapy must continue for an indefinite period. Unless the first symptoms are due to a complication, such as perforation, an ulcer in its early stages should always be considered potentially susceptible to dietetic and medicinal treatment. Many superficial erosions or mucous ulcers heal spontaneously; many others heal rapidly and permanently after rest, regulation of diet, and medicinal therapy; but when the ulceration is deep, when it reaches the level of Auerbach's plexus, or when it is associated with the formation of a large amount of scar tissue, surgical treatment, although not uniformly successful, may be much more satisfactory than medical treatment. If employed before the lesion advances far, the possibilities of hemorrhage, perforation, or perigastric adhesions are in large measure avoided.

Medical-dietetic Treatment.—The three essentials of the medical treatment of ulcer are: to provide at least partial rest for the stomach by eliminating both physical exertion and mental strain; to regulate the diet suitably; and to relieve the pylorospasm and gastric irritability, to control constipation, and correct gastric hypersecretion by administration of drugs. If there is noteworthy bleeding, absolute rest is necessary. A cheerful atmosphere is indispensable. Although hospital treatment is generally more satisfactory, the patient should remain at home if it involves great financial sacrifice and consequent worry.

Diet.—In the regulation of the diet there are three requirements: to eliminate all food which can irritate the stomach mechanically or otherwise; to include foods which can hold considerable acid in combination, as well as those which call forth only slight or minimal secretion of gastric juice; and to provide material which will build up the patient and facilitate healing of the ulcer and return of the blood to normal. The relative importance of these factors varies in different cases. Since white of egg, olive oil, salt-free butter, and gelatin evoke practically no gastric secretion, they may at first be given exclusively in certain cases at one- or two-hour intervals. Most patients, however, object to this diet, which is theoretically almost ideal. Consequently, in practice, milk and cream, or cereal, or, preferably, a combination of the two are more satisfactory. Although many physicians advocate hourly feeding (90–100 c.c. of a mixture of milk and cream in equal parts, or a thick cereal gruel) from 7 or 8 A. M. to 8 or 9 P. M., most patients

seem to improve more rapidly if the intervals are lengthened to two or three hours, and the amount of each feeding correspondingly increased. For many patients, six meals at three-hour intervals (at 7 A. M., 10 A. M., 1 P. M., 4 P. M., 7 P. M., and 10 P. M. for example) consisting of between 6 and 8 ounces of milk, milk and cream, or cereal gruel, prove best for the first one or two weeks. To this may be added boiled rice, custard, soft eggs, milk toast, bread which must be thoroughly chewed, butter, the alimentary pastes, purée of green vegetables, and sometimes, after two or three weeks, such meats as chicken, lamb chops, and fish. For the last three or four weeks, three soft meals may be chosen from the above, and milk and sometimes cereal gruels taken between meals and at bedtime. In spite of the fact that most subjects take fruit juices and stewed fruits well, a considerable proportion have greater discomfort after ingestion of fruit in any form. It should, therefore, be administered with care. Excess protein (Lenhartz diet) is not usually desirable, but after severe hemorrhage it seems to be suitable, presumably because of its upbuilding properties. Unless there are complications, four to six weeks of this régime combined with complete or partial rest and the proper medication completely relieve symptoms. If the patient is to be *cured*, however, this initial and intensive treatment must be followed by strict adherence to the proper diet for many months or, practically, indefinitely. Regular meal hours, leisure at meal time, slow eating, thorough mastication, and avoidance of all irritating foods and drinks (coarse foods, especially coarse raw foods, highly seasoned substances, condiments, meat extractives, acids, very hot and very cold foods or drinks, alcohol, and in many cases coffee, tobacco, and salt) are also essential in the after-treatment. The success of the dietetic cure depends upon the ability of the physician to persuade his patient of the necessity of carrying out these dietetic directions for a very long time.

If there is *hemorrhage*, starvation for a few days and administration of water, soda, and glucose by rectum are necessary. *Intractable vomiting* demands similar treatment, or, occasionally, if very persistent, feeding through the duodenal tube in order to provide more calories than can be given successfully by rectum. Rectal injections relieve thirst and lessen the chance of acidosis.

Medication.—In the medicinal treatment of ulcer *alkalies* have always played the largest rôle, the most useful being bismuth subcarbonate, calcinated magnesia, milk of magnesia, calcium carbonate, and sodium bicarbonate. These are usually more helpful in combination than separately. Administration of from $\frac{1}{2}$ to 1 teaspoonful of a mixture of equal parts of soda and bismuth, soda and lime, or soda, bismuth, and calcinated magnesia from one to two hours after each feeding, and of one or two additional doses during the night if there is nocturnal pain, is usually more efficacious than the hourly administration of somewhat smaller doses, as is frequently advocated. Although generally magnesia is used when there is constipation, calcium when there is diarrhea, quite a few patients cannot take magnesia without augmenting their discomfort. In such individuals, constipation can be alleviated by a morning dose of Carlsbad salts or of a similar saline laxative taken in hot water on waking, or by ingestion of mineral oil or a simple vegetable laxative at night. Whether the continued use of alkalies decreases the activity of the gastric glands is questioned, although the weight of evidence is in favor of it, especially in the case of

magnesia and soda. In certain patients with *pain*, very much larger doses of bismuth (a heaping teaspoonful of the subcarbonate or subnitrate several times a day, or a tablespoonful in the early morning) often give relief, but. as a rule, the drug which most satisfactorily relieves pain that is not greatly alleviated by rest, diet, and alkalies, is belladonna or its alkaloid, atropin. These are particularly effective when there is marked lack of balance between vagus and sympathetic. The drug must be taken in maximal doses, the exact size of which is determined by administering a small initial dose (5 drops of the tincture of belladonna t. i. d. before meals) and increasing the dose 1 drop every day until the limit of tolerance is reached. Some patients can take as much as 30, 40, or even 50 drops t. i. d. If the patient is very nervous, small doses of *bromid* (10 to 15 grains t.i.d., preferably strontium bromid) may be given alone or in combination with *hyoscyamus* (10 to 20 drops of the tincture). The great relief of symptoms which sometimes follows an *x*-ray examination suggests that it may be beneficial to give occasionally, in refractory cases, large doses of some *bland powder* (2 to 4 ounces of barium sulphate, bolus alba, neutralon, etc.). The fundamental part of treatment, however, after removing in so far as possible all contributory factors, such as infections, nervous strain, and unhygienic habits, is to provide rest for the stomach and the appropriate diet. Often this alone is sufficient, but usually alkalies, and, in a considerable number of cases, belladonna must be used to relieve symptoms and bring about potential cure.

Cohnheim strongly recommends *olive oil* (℥j–iv p. c. or ℥ss–j every morning), and it does seem to be really helpful when it can be taken without distaste. The *silver salts* formerly used so much are no longer employed to any extent, although occasionally a pill of silver nitrate (gr. $\frac{1}{4}$–$\frac{1}{2}$) relieves pain when other measures fail. Recently colloid silver has been administered by certain physicians.

Subcutaneous, intramuscular, or even intravenous injection of *nonspecific protein* has been followed with some success. The basis for this type of therapy, *i. e.*, the belief that ulcers are due to a trophoneurosis, is also the foundation of the employment of *sympathectomy* in treatment. This is thought to relieve pyloric spasm and angiospasm, which, in reality, demand more treatment than any other manifestations of ulceration.

Treatment of Symptoms.—For slight *pain*, rest, application of an ice-bag, and proper regulation of diet is all that is necessary. Atropin may be given hypodermically or dissolved under the tongue ($\frac{1}{200}$–$\frac{1}{100}$ gr.); or in combination with bismuth subcarbonate or subnitrate. One or two large doses of bismuth (℥ss–j) may be administered, or small amounts (℥j or ij) every two to four hours. If there is much nervousness, the bromids or hyoscyamus are helpful. When the pain does not yield to such medication, codein, anesthesin, or even morphin or pantopon may be given.

Hemorrhage demands absolute rest, application of an ice-bag to the epigastrium, complete starvation, and the hypodermic injection of morphin. Unless the bleeding is severe, these measures, as a rule, suffice when supplemented with administration of water, glucose, and soda by rectum, either by the Murphy drip method or by repeated small enemata (300 to 500 c.c. every six hours). If the symptoms increase, transfusion of blood is advisable; in certain cases this may have to be repeated several times. When properly grouped blood cannot be quickly obtained, 10 c.c. of horse-serum

may be injected if the patient has not been sensitized by previous administration (diphtheria antitoxin). When bleeding is very slight and shown only by the presence of occult blood in the stool, ambulatory treatment is permissible. Certain patients for whom absolute rest is impossible improve surprisingly under a régime including partial rest, restriction of diet to simple foods, and appropriate medication. As a rule, however, this is not safe.

If the patient is in a state of collapse when first seen, coffee or alcohol may be added to the fluid given by rectum, camphor or caffein injected hypodermically, and a salt infusion given while a blood donor is being sought. In most cases, however, absolute rest, local application of cold, starvation, and administration of morphin are all that is necessary. White of egg or cereal water can usually be given on the third, fourth, or fifth day; as the patient progressively improves, the diet may be gradually increased. If regeneration of blood is very slow, and hypodermic injection of iron and arsenic (iron cacodylate) seems to have little or no effect, repeated transfusion of small amounts of blood may be necessary. The various drugs supposed to promote coagulation appear to be quite ineffective.

After the acute symptoms are over and the patient feels well, it is very difficult to make him realize that, to prevent a recurrence, the simple regimen must be continued for a very long time. Unfortunately, such persistence is not agreeable to most patients and many potential cures are sacrificed because of the impatience of the subject and the lack of insistence by the physician. Successful "cure" of an ulcer is comparatively easy, but very few physicians can so inspire their patients that they are willing to continue for many months the measures which prevent recurrence.

Surgical Treatment.—When recurrences repeatedly follow medical treatment, when there have been severe hemorrhages, when there are signs and symptoms of progressive pyloric obstruction, when hypo-acidity and the persistent presence of occult blood in the feces suggest possible malignant degeneration, and when there are evidences of extensive adhesions which produce constant pain or so deform the stomach that it is unable to function properly, surgical treatment is necessary. Of course, immediate operation is demanded by perforation.

Cicatricial pyloric or duodenal stenosis results from organic obstruction and the associated spasm. In many cases such stenosis is at first complicated by a true muscular hypertrophy of the stomach, which for a considerable length of time compensates for the obstruction. When peristalsis becomes visible, however, when large food residues are vomited and there is excessive hypersecretion, and many sarcinæ are present in the gastric contents, it is very unwise to delay surgical intervention. It is in this type of case, in which large quantities of acid are lost by vomiting, that *gastric tetany* develops. This condition may be treated successfully by intravenous injection of calcium chlorid or calcium acetate (50 to 75 c.c. of a 2 per cent. solution, or 10 to 15 c.c. of a 10 per cent. solution).

Perigastritis, often with adhesions to other organs, such as the gall-bladder, intestine, and pancreas, may so disturb gastric function as to necessitate operation. The danger of the formation of new adhesions is minimized by careful technic and proper insertion of the omentum between raw surfaces.

Suspicion of a *transition to cancer*, which occurs probably in from 5 to 10

per cent. of chronic gastric ulcers, practically never in duodenal ulcers, always warrants surgical treatment. A steady drop in the acid readings, persistence of occult blood in the stool, and, as a rule, a small appetite and loss of weight and strength are the diagnostic signs.

Hour-glass (bilocular) and *multilocular deformation of the stomach*, either as the result of cicatricial contraction or spasm at the ulcer level, or both, often require surgical treatment.

Perforation demands immediate surgery. The success of treatment depends upon the brevity of the interval between perforation and operation. A large percentage of patients operated on four to six hours after perforation, recover; but every additional hour increases the mortality rapidly. Although sometimes closure of the perforation is all that is possible, a gastro-enterostomy is desirable if the patient's condition permits, for postoperative stenosis is liable to occur. If the perforation opens into the lesser peritoneal cavity, an abscess may develop which requires surgical evacuation. *Spontaneous pneumoperitoneum* after acute perforating ulcer has been demonstrated by the *x*-ray.

Every chronic or callous ulcer which resists medical-dietetic treatment should also be treated surgically, although in many cases a perfect cure is not possible. No operation as yet devised establishes really physiological conditions. Finney's pyloroplasty or gastroduodenostomy accomplishes this most nearly. *Resection of the stomach*, with removal of the ulcerative area, is considered the most desirable operation by many surgeons; the mortality is surprisingly low. On the other hand, Balfour, whose method of cauterization is certainly advisable for small ulcers high on the lesser curvature, believes, "that there is no operation more useful than *gastro-enterostomy* in cases of chronic duodenal ulcer, except in carefully selected cases. The operation in suitable cases can be depended on to give excellent and permanent results in more than 90 per cent. of the cases." Probably the greater the degree of pyloric or duodenal obstruction, the more brilliant the results of gastro-enterostomy; in cases without obstruction the results are, in the main, unsatisfactory, although the constant reflux of alkaline intestinal contents unquestionably helps relieve the symptoms due to hyperacidity. The intestinal indigestion of varying severity can be materially diminished by careful dieting for a long time after operation. The success of all forms of operative therapy for ulcer is often jeopardized or almost nullified by the lack of appreciation on the part of the surgeon of the importance of prolonged adherence to a bland diet after operation. The incidence of jejunal or marginal ulcer after gastro-enterostomy varies according to different observers from 1 and 2 per cent. to more than 5 per cent.

One may say, however, that whether the operation be a pyloroplasty, a gastro-enterostomy, or a resection, surgical treatment offers a greater chance of success than blind medical treatment when the condition is advanced. "The dangers of medical treatment are very formidable and the mortality far greater than with surgical treatment" (Moynihan). Although potential medical cure is often sacrificed because of the unwillingness of the patient to live on a carefully restricted diet for a long time, and surgery is, therefore, employed for lack of better measures, it is very unfair not to give the patient the possible benefit of surgery. In about 60 per cent. of gastric ulcer cases, 70 per cent. of duodenal, and more than 75 per cent. of cases with marked obstruction the patient has considered himself practically well three years

or more after various operations. Pyloroplasty or gastro-duodenostomy, which are possible in more than 50 per cent. of cases, are the ideal operations. Gastro-enterostomy should be employed only when these are impossible because the duodenum cannot be mobilized. Its success stands in direct relation to the degree of pyloric or duodenal obstruction; if this is very marked, the results are generally striking. Excision of the ulcer is not successful in most cases—probably in not more than 20 per cent.

THOMAS R. BROWN.

CANCER OF THE STOMACH

(Scirrhus, Medullary, and Colloid Cancer, and Linitis Plastica)

Incidence.—Cancer of the stomach, next to that of the uterus, is the most common type. In Rodari's series it was observed at 2 per cent. of all autopsies. The general belief that cancer is on the increase is probably correct, in part at least, because the average length of life is steadily increasing and cancer is usually a disease of later life. Nevertheless, some of the reported increase may be accounted for by the ever-growing interest of both laity and physician in the disease, and by the improvements in methods of diagnosis.

Cancer of the stomach is almost always primary; the rare secondary form, in more than 50 per cent. of cases, follows cancer of the breast. Occasionally the lesion is a direct extension of disease from the liver, gall-bladder, pancreas, or intestine. Cancer of the stomach occurs somewhat more frequently in men than in women, and usually develops in individuals between forty and seventy years of age. The occasional cases seen in younger patients run a very rapid course. Heredity seems to predispose a certain number of individuals to the disease. In certain localities the incidence is markedly higher than in others, in northern France, for instance, and broadly speaking, in the more northern countries. Meat-eating peoples are more subject to the disease than vegetarians.

Etiology.—The cause of cancer is not known, but there is considerable evidence that chronic irritation may play an etiological rôle in certain cases. Many believe that *chronic gastritis* leads to carcinoma, but probably the reverse is almost always true, *i. e.*, practically every gastric cancer after a certain length of time leads to chronic gastritis and often to atrophic gastritis with achylia. In only 5 to 10 per cent. of the cases of *chronic gastric ulcer* does malignant degeneration take place, and lesions of this origin comprise not more than 15 per cent. of the total number of gastric cancers. Kussmaul insists that in the majority of cases the disease develops without previous digestive disturbances. A few cases develop from *polyadenoma*. *Syphilis* has been considered an etiological factor, but without suitable evidence. A gumma of the stomach may simulate gastric cancer, and gastric cancer may develop in a syphilitic patient, but there does not appear to be any causal relationship between the two. Lane believes that cancer is often due to *intestinal stasis* and *autotoxemia;* that it is a disease of civilization

produced by the elimination of coarse, bulky, uncooked food from the diet; and that the larger dependence upon such foods and the almost complete abstinence from meat accounts for the striking immunity of primitive peoples.

Morbid Anatomy.—In a large series of cases the site of the carcinoma was in the pylorus in 35 per cent., the cardia in 25 per cent., the lesser curvature in 16 per cent., the entire viscus in 13 per cent., the greater curvature in 5 per cent., the anterior wall in 4 per cent., and in the posterior wall in 4 per cent.; but this was observed when the cancer was in its later stages at operation or autopsy, when the growth was extensive, and not in the same position as during the earliest phase. The more the condition is studied, the more apparent it becomes that cancer usually originates in the lesser curvature, whence it extends to the pylorus, cardia, or even a large portion of the stomach, and produces very different clinical types. An *initial lesion* at the pylorus, cardia, or anterior or posterior wall is comparatively rare. This predilection for the silent area (the lesser curvature) and avoidance of the pyloric or cardiac orifices renders early diagnosis of cancer of the stomach very difficult. Consequently, a fair chance of success with surgical therapy is possible in only a small minority of cases, *i. e.*, in those originating in the pylorus or cardia, and in those secondary to chronic ulcer.

Types.—Cancer of the stomach may be of several types. *Scirrhus carcinoma* with extensive connective-tissue formation is sometimes associated with *linitis plastica* which was formerly regarded as benign, but is now usually considered an acellular type of scirrhus cancer with excessive connective-tissue proliferation. Usually a large number of serial sections must be examined before the cancer cells are found. *Medullary* or alveolar lesions are very cellular, prone to rapid growth and early degenerative changes, and are sometimes encephaloid in character. *Colloid cancer*, the rarest type, is the only one for which deep *x*-ray therapy seems to have been at all successful.

In the very cellular type ulceration is early; in the scirrhus type and in linitis plastica, relatively late. Usually if the lesion is advanced, the rest of the stomach shows evidence of chronic gastritis, and it is not uncommon to find benign ulceration in the neighborhood of the growth. This presumably results from the disturbance of blood-supply, but is erroneously regarded as a precursor of malignancy. The mucous membrane is often covered with erosions or ecchymoses. In certain cases of medullary carcinoma the growth is extremely vascular (fungus hematoides).

The growth and extension of the neoplasm may alter the whole contour of the stomach. Cardiac cancer may markedly contract the stomach; pyloric carcinoma may cause marked dilatation, and cancer of the body of the organ produce hour-glass, multilocular, or various other deformities. In *linitis plastica* the stomach is usually reduced to a narrow rigid tubular organ of very small caliber (leather-bottle stomach). The cancerous growth practically never invades the duodenum.

In a few cases cancer of the stomach extends directly to other adjacent organs, but usually the disease is carried through the lymphatics or the blood-vessels. Such metastases are most often seen in the lymphatic glands, especially the contiguous mesenteric glands and the liver. Involvement of the left supraclavicular gland, which is very rare, is of classical interest

and great diagnostic value. The occasional metastases in the *cul-de-sac* of Douglas emphasize the importance of a rectal examination in all suspected cases.

Enlargement of the glands may be caused *not* by metastasis, but by secondary or tuberculous infection. Consequently, such glands should always be studied histologically to indicate the prognosis. Adhesions often form in the late stages between the stomach and neighboring organs (liver, pancreas, colon) and are sometimes invaded by the cancerous growth.

In a general way the course of cancer is closely related to the histology; rapid progression, early ulceration and hemorrhage, toxemia, and cachexia are characteristic of the very cellular type; while in scirrhus cancer and *linitis plastica* progress, as a rule, is slower, and many of the symptoms are the result of the associated motor disturbances.

Symptoms.—There are no *early* symptoms characteristic of gastric cancer. Those commonly seen constitute three different syndromes which vary markedly. The *first*, which is by far the most common, begins insidiously, usually after singularly few digestive disturbances, and the immediate cause is sometimes thought by the patient to be an especial indiscretion in diet; the *second* type of syndrome gradually and almost imperçeptibly develops from that of prolonged chronic gastritis or other functional dyspepsia; and the *third* is that of *ulcus carcinomatosum* which gradually follows the classical manifestations of gastric ulcer. In the first and most common type the history is of fundamental importance, and the unexplained appearance of vague digestive symptoms, such as discomfort after meals, a slight diminution in appetite, a little loss of strength and weight in middle-aged or elderly individuals, and sluggish response to symptomatic treatment, should always suggest the possibility of gastric cancer and indicate the necessity for intensive examination. The blood and gastric contents should be examined at once, the presence or absence of occult blood in the feces ascertained, and *x*-ray plates carefully made. If thorough investigation of habits and of the general physical condition fails to reveal any cause for the abnormal gastric digestion, if the symptoms do not yield to appropriate treatment, and if the results of the tests mentioned above are at all suggestive, early exploratory operation must precede definite diagnosis. This prevents the delay in determining diagnosis, which may render later operative treatment unsuccessful.

Ulcus carcinomatosum is usually preceded by a long, typical, or atypical history of chronic *gastric* ulcer, with its characteristic punctual and periodic symptoms. As a rule the appetite gradually decreases; in some cases patients become slightly pale and weak; the discomfort is constant; the acid content of the stomach lower; and occult blood is persistently present in the stools, however bland the diet. Every attempt should be made to establish diagnosis relatively early, while acidity although diminishing is still high, for it is this type of gastric cancer which offers the best chance for relatively early diagnosis and successful surgical cure. If the growth begins at the cardia, *dysphagia* is the early symptom, while if it begins at the pylorus, *symptoms of obstruction* develop early. As a rule, however, the growth begins on the lesser curvature, and obstructive symptoms are consequently a relatively late manifestation of the disease. When the *body of the stomach* is involved and neither orifice affected, the growth may, in certain cases, become very large without producing striking or characteristic symptoms.

Although many symptoms are thus largely dependent on the site of the growth and its influence on the motor mechanism of the stomach, others depend on its effect upon the gastric secretions, the loss of appetite, the associated toxemia and anemia, and on the presence or absence of metastasis or extended growth in the neighboring organs.

The following is a consideration of the important symptoms, many of which are often late or absent:

A *lack of appetite*, especially for meat, often becomes a profound anorexia in the later stages of the disease. When the lesion is in the lesser curvature this may be a late manifestation. *Thirst* is often marked with pyloric or cardiac involvement.

The usual *dyspeptic symptoms* of fulness and discomfort after meals, with acid eructations, are not in the least characteristic, but often become very marked in the later stages. Their appearance in middle-aged individuals without cause should always arouse suspicion.

Pain is not characteristic, and is often absent, especially in the early stages. It is usually present, however, and sometimes severe if the orifices are involved, in *ulcus carcinomatosum*, in cases with perigastric adhesions, and in the later stages of the disease. *Ulcus carcinomatosum* is the only type of gastric carcinoma commonly associated with early pain.

Vomiting is common with involvement of cardia or pylorus. In the former case, it occurs almost immediately after ingestion of food; in the latter, after an interval. It is sometimes cumulative, especially when marked gastric atony has developed. The vomitus is often very abundant, very foul, contains food eaten a long time before, and frequently settles into three layers. Changed blood, fatty acids, infusoria, flagellates, and even bits of cancer tissue can be found in it under the microscope, and characteristic bacteria (the Oppler-Boas bacilli). While the presence of lactic acid and these bacilli is simply the result of fermentation in a stomach with obstructed pylorus and lack of free hydrochloric acid, these signs are important because in most, but not in all cases (*e. g.*, lues, benign neoplasms), such obstruction is malignant.

The *gastric contents* are frequently abnormal. In more than 75 per cent. of cases free hydrochloric acid is absent, and while only 5 to 10 per cent. of achlorhydrias as shown by the ordinary Ewald test-meal are due to malignancy, this sign is of value in connection with others. At times this achlorhydria of cancer results from associated chronic gastritis, but frequently it must be due to the effect of some toxin upon the secretory cells, or possibly to an autolytic ferment secreted by the cancer cells which by proteolysis form bases with a marked affinity for hydrochloric acid. The increased quantity of soluble protein in the gastric contents of patients with cancer may be demonstrated by the Wolff-Junghans test. The presence of *lactic acid* is merely a sign of stagnation of the gastric contents in the absence of hydrochloric acid.

Tumor, the most characteristic manifestation, must be distinguished from gumma, dense ulcer cicatrix, and extragastric tumor. As a rule they do not follow the respiratory movements. Carcinoma of the *cardia* is not palpable, but produces symptoms of progressive dysphagia which are very suggestive. This type can be demonstrated through the esophagoscope. So-called *primary* cardiac carcinoma is usually carcinoma of the lower end of the esophagus.

Unless gastroptosis is marked, carcinomatous tumors of the lesser *curvature* cannot usually be palpated until they have become relatively large. With deep inspiration palpation of the abdomen under a hot bath or with the patient lying on the right side sometimes permits such lesions to be felt in comparatively early stages. Inflation of the stomach often renders tumors of the *anterior wall* more palpable. In *pyloric cancer* the hard nodular tumor is usually easily felt; it is sometimes visible, and often associated with visible peristalsis. In *linitis plastica* a tubular or pipe-like mass may be felt which is usually rather smooth and contrasts with the hard, irregular, nodular tumors of most other types of gastric cancer. When growths are palpable they are usually of relatively large size. The most common form—that of the lesser curvature—especially when it occurs in the so-called herbivorous type of individual with wide costal angle and capacious hypochondrium, may attain remarkable size before becoming palpable.

The gastroscope has not proved of great help in the demonstration of gastric neoplasms, but the *x*-ray is invaluable. It does not, however, do away with many sources of error. In some cases artificial pneumoperitoneum facilitates *x*-ray examination.

It is not unusual for a metastasis in the liver, omentum, or *cul-de-sac* of Douglas to be palpable, or for a spinal metastasis to be manifest before the primary growth can be felt.

Bleeding is very common, but large hemorrhages are rare. Almost always *occult blood* is persistently present in the feces, however bland the diet. This is one of the greatest aids in the diagnosis of doubtful cases, even in the early stages, when there is no demonstrable source of bleeding in mouth or rectum.

Cachexia, which consists of inanition, malnutrition, and anemia, and is possibly caused in part by toxemia, is a suggestive but often very late sign of gastric cancer. Gradual loss of fat and muscle; increasing pallor; progressive anemia, usually of the secondary type with slight leukocytosis, but occasionally identical with that of pernicious anemia; a constant loss of nitrogen; increasing weakness; dyspnea; sometimes increasing nervousness; and often in the very late stages increasing apathy, are typical manifestations. The weight may be less than 50 per cent. of the normal.

Among the signs and symptoms not usually employed for diagnosis are an increase in the quantity of antitrypsin in the blood, of colloid nitrogen in the urine, and the results of various serological tests. *Fever* is not usual in the early stages, but not rare when the disease is advanced. Occasionally the temperature becomes very high. *Albuminuria* is not unusual. *Myocardial symptoms* frequently accompany marked anemia; and *edema* sometimes develops in the later stages.

The course of carcinoma is progressive and modified or accelerated by *complications*. The most important of these are involvement by metastasis or direct extension of such organs and tissues as the liver, mesenteric glands, and peritoneum; and the development of perigastric adhesions. Peritoneal involvement is often accompanied by ascites, the fluid usually being stained with blood. In the late stages of the disease secondary infection with pyogenic bacteria may cause pyelitis and abscesses in the liver or other organs.

In the rare cases *in the young* the course of the disease is very rapid

Extensive hemorrhage is relatively rare, perforation very uncommon. In certain cases gastric cancer produces only intestinal symptoms which suggest intestinal cancer. The most striking symptoms of *linitis plastica* are those due to the constant reduction in the capacity of the stomach and the consequent persistent vomiting or hypermotility. These, with *x*-ray evidence and the presence of a long tubular palpable tumor, suffice for diagnosis. The lesion may involve the entire stomach or may be localized in the pyloric and prepyloric region; occult blood is often absent; and metastasis occurs very late. Differentiation of the localized linitis from the cicatricial stenosis which follows ulcer is practically impossible.

Diagnosis.—Nothing is easier to diagnose than gastric cancer in the late stages. The palpable tumor, the anemia, anorexia, cachexia, emaciation, gastric achylia, and characteristic filling defect demonstrable in fluoroscopic and radiological studies are all typical. But *early diagnosis*, which is essential for permanent cure, is extremely difficult. Most carcinomatous lesions do not develop from ulcers, but originate in the lesser curvature (the silent area) where the tumor cannot be felt; obstructive phenomena do not occur; and digestion is but slightly impaired for quite a while. It is, therefore, wise to suspect all dyspepsias which originate in middle or later life without cause, and do not yield promptly to symptomatic treatment. If thorough examination reveals no cause and careful treatment proves useless after about a month, exploratory laparotomy should be performed so that the growth may be removed even before diagnosis can be made definite. Low or falling acid content, achlorhydria, slight anemia, the persistent presence of occult blood in the stools, a small filling defect revealed by the *x*-ray, slight loss of appetite, and loss of weight and strength, all indicate at least a provisional diagnosis. If the growth begins in the cardia or pylorus, early symptoms of obstruction develop. It is better to operate because of a well-grounded suspicion than to postpone operation until diagnosis is assured and surgical treatment practically useless.

In the *differential diagnosis* old callous ulcers, gumma, gastritis, disease of the gall-bladder, extensive perigastric adhesions, and pernicious anemia are most difficult to distinguish. In *ulcer* the appetite, as a rule, is good, the acid content of the stomach usually but not always high, and occult blood often absent after careful dietetic treatment. In *subacid* or *acid gastritis* or *functional achylias* (more than 90 per cent. of the achylias are benign) the history, the obvious causative factors, the absence of occult blood in the stools, the negative *x*-ray findings, and the fact that the quantity of soluble protein in the gastric contents is smaller than in cancer, usually permit diagnosis. Pernicious anemia and cancer of the stomach are sometimes confused because of the severe anemia which characterizes both conditions. In cancer, however, the red cell count is rarely so low as in pernicious anemia. A low color index and the absence of nucleated red cells are more suggestive of cancer. On the other hand, the negative *x*-ray findings, the lack of loss of weight, the negative Wolff-Junghans test, the positive Van der Bergh test, all suggest pernicious anemia. *Perigastric adhesions* caused by ulcers or disease of the gall-bladder may sometimes produce a puzzling condition, especially in *chronic disease of the gall-bladder* in which such adhesions may produce a persistent filling defect. Achylia is the rule in these cases. The history and the absence of occult blood in the stools are helpful, but diagnosis is often rendered even more difficult by the fact that

the disease occurs as a rule at the same time of life as cancer and is often associated with a striking lack of appetite and loss of weight.

Diagnosis is never complete until the possibility of *gastric lues* is considered, especially when symptoms are somewhat atypical, and the achylia, the palpable tumor (gumma), or large filling defect, the great loss of weight, and sometimes the presence of occult blood make the diagnosis difficult. A Wassermann test should always be made before the final diagnosis of cancer is made. A positive reaction, however, obviously does not preclude carcinoma, but merely suggests the advisability of observing the effects of specific antiluetic treatment before making the diagnosis of cancer.

Treatment.—Surgery offers the only hope of cure. In gastric cancer radium and deep *x*-ray therapy have proved singularly disappointing, but in the rare colloid carcinoma such treatment sometimes seems to arrest the disease temporarily. To be successful the operation must be performed relatively early. Even in advanced cases, however, when there is no evidence of extensive metastasis, partial resection and even complete gastrectomy are justifiable, especially in scirrhus carcinoma and *linitis plastica*. Exploratory laparotomy should not be performed to verify diagnosis or to accentuate a hopeless prognosis unless radical surgery is permissible whenever there is *any* hope of resection prolonging life or leading to cure. For extension or metastasis of the growth purely palliative operations are usually advisable; *i. e.*, gastrostomy for cardiac and gastro-enterostomy for pyloric neoplasm with obstruction. Very marked temporary improvement and considerable prolongation of life often follow these operations. To render surgical treatment of greatest benefit operation must take place in the early stages. This is possible if the development of symptoms suggesting malignant degeneration is constantly looked for in chronic gastric ulcer, if the unexplained dyspepsia of middle or later life is suspected to be a manifestation of cancer, and if surgery is advised before a definite diagnosis can be made.

As the majority of patients ask for treatment so late that operative measures are not justifiable, medical-dietetic treatment is necessary to render the patient as comfortable as possible for the few remaining months of life. *Lavage* for obstruction, and administration of a *diet* arranged to fill the needs of each patient, which is at first light and without meat, then soft, later liquid, and, finally, composed, during the terminal stages, of fluids and foods with little or no residue (egg-white, beef juice, fruit juice, glucose solution, clear broth, cereal water, and alcohol). In other words, the thirst should be relieved; the minimal amount of strain imposed on the stomach; and an attempt made to prolong life by administration of sufficient calories. The latter is usually impossible and is of far less importance than the minimization of discomfort and pain. Tap-water mixed with soda and glucose often helps to relieve thirst when given by rectum and lessens the chance of acidosis. So-called nutritive enemata are practically useless. If the patient or the patient's family demand specific treatment, radium or deep *x*-ray therapy or intravenous injection of certain colloidal metals (Wassermann's colloid selenium) may be tried, although in many cases such measures increase the discomfort of the patient. In very few do they produce even temporary improvement.

Treatment by drugs is purely symptomatic. *Hydrochloric acid* very occasionally seems to lessen the dyspeptic symptoms. Tonics, strychnin,

caffein, digitalis, and cacodylate of soda or iron (hypodermically) may be given. Bitters sometimes produce a temporary euphoria. Laxatives must be given when necessary. Practically always, especially in the later stages, sedatives are necessary; they must be more and more potent and given in increasing amounts. Belladonna, bismuth, and the bromids may be employed first; then anesthesin, pyramidon, or aspirin; and finally, unless death is caused by intercurrent affection, some form of opiate is necessary (codein, morphin, pantopon, dionin, Schlesinger's solution, etc.). These opiates should usually be given by suppository or hypodermic injection, as absorption may not take place in the stomach.

THOMAS R. BROWN.

OTHER GASTRIC NEOPLASMS

While medullary, colloidal, and scirrhus cancer of the stomach are relatively common, other gastric tumors are extremely rare. Among those seen are sarcoma, myoma, fibroma, fibromyoma, hemangioma, lipoma, lymphadenoma, polyadenoma, gastric pseudoleukemia, and also the interesting foreign body tumors (hair-balls) occasionally seen in hysterical patients. They are very rarely diagnosed correctly, and are either found when they produce no symptoms, or are incorrectly considered gastric cancer. Although their true nature is usually only determined at operation or autopsy, careful analysis shows that almost always there is some unusual or atypical sign or symptom which should arouse suspicion. The general health may be better than with a true carcinoma; there may be tremendous hemorrhages and complete absence of blood, even of occult blood, from the feces between the periods of bleeding; atypical symptoms of obstruction sometimes develop; the gastric chemistry becomes unusual, and *x*-rays reveal atypical conditions—an encapsulated shadow, a shadow-like air bubble in the stomach wall, and a lesion far more clearly outlined than those typical of gastric cancer. Extensive, often exsanguinating hemorrhages, followed by rapid recovery of health, strength, and normal conditions in the blood, and negative stool findings should always suggest the presence of a benign or relatively benign tumor, polyp, hemangioma, or a relatively benign sarcoma.

Sarcoma may occur in individuals less than twenty years old, but is more common in those between thirty and forty. The tumor is likely to affect the body of the stomach and may be infiltrating or encapsulated; it is prone to periodic hemorrhages, or, in some cases, to steady bleeding which makes the blood resemble that of pernicious anemia; often undergoes late metastasis; and although sometimes on palpation and in *x*-ray study it seems to be extragastric, is usually mistaken for an hepatic cyst or abscess, ovarian cyst, floating spleen, or mesenteric glandular tumor. Surgery is often a successful treatment for the encapsulated type.

Development of *benign tumors* from the glandular tissue results in polyadenoma. Sometimes the masses are large. Polypoid tumors are the most interesting type, especially when they ulcerate and produce a bleeding

syndrome very suggestive of cancer. At times true cancerous transformation may take place. *Gastric myoma* is a very rare condition which was first described in 1762. Virchow divides it into the subserous and submucous types. The tumor may become very large (6 kilos) and pedunculated, cause attacks of severe pain and vomiting, and lead to great emaciation, but the most striking symptom is usually hematemesis. A small proportion undergo malignant degeneration. *Lymphadenoma* may occur in leukemia, while in *pseudoleukemia* enormous hyperplasia of the gastro-intestinal lymphoid tissue takes place in about 3 per cent. of cases (pseudoleukemia gastro-intestinalis). The clinical course of this disease is very like that of gastric cancer. The histological changes suggest the relatively benign type of lymphosarcoma.

The *treatment* of these gastric neoplasms is surgical; the *prognosis* is good in the pedunculated or encapsulated form and less favorable in the infiltrating types.

THOMAS R. BROWN.

GASTRORRHAGIA

(*Gastric Hemorrhage*)

Gastric hemorrhage is obviously not a disease *sui generis*, but merely a sign or symptom. It is, however, of such importance that it requires special consideration.

Etiology and Pathogenicity.—Of the manifold causes the most important are:

(1) Various forms of *trauma*, such as wounds of the stomach, severe blows upon the abdominal wall, and the swallowing of various substances. As a rule cure is spontaneous or the patient dies. Such lesions rarely seem to be the starting-point of ulcer.

(2) *Corrosive poisons*, mercury, phosphorus, etc. The vomiting of blood-stained fluid is often the first symptom of bichlorid of mercury poisoning.

(3) Various *ulcerative gastric lesions*. These are the most common cause. (*a*) *Simple peptic ulcer* is the most important cause of gastric hemorrhage and often produces very abundant bleeding which bears little or no relation to the size of the ulcer. Hemorrhages, as a rule, are larger in the acute than in the chronic callous form; in either case they are sometimes so slight as to be demonstrable only by the presence of occult blood in the stools. Usually, but not always, hemorrhages cease when the symptoms of ulcer disappear. This is a fair index of the efficacy of treatment. (*b*) *Various gastric neoplasms*. Gastric cancer causes less severe bleeding than gastric ulcer, and the hemorrhage, as a rule, is constant, irrespective of treatment. The persistent presence of occult blood in the stools, when there is no bleeding from mouth or rectum, is most suggestive of gastric neoplasms. *Gastric sarcoma, hemangioma*, and *polyp* may all be associated with severe hemorrhage. The author has seen 2 cases of sarcoma in which the patient was almost exsanguinated. (*c*) Rare *tuberculous* and *syphilitic* gastric lesions

sometimes produce bleeding, usually of the occult type. In syphilis this symptom is often absent, but occasionally it is very severe. (*d*) *Various diseases*, such as nephritis, especially in its later stages. There may be very diffuse gastric ulceration. (*e*) Acute gastritis, particularly the toxic type, sometimes causes severe hemorrhages. More frequently, however, the bleeding is slight and associated with multiple erosions. Its association with chronic gastritis is not common.

(4) *Hepatic diseases.* The very severe gastric hemorrhages which occur in many diseases of the liver are usually due to obstruction of the portal circulation and consequent varicosity of the gastric veins, often associated with esophageal varices. In some cases the supposed gastric hemorrhage may be entirely esophageal. In *Laennec's cirrhosis, biliary cirrhosis, Banti's disease*, and *pylephlebitis* bleeding may be severe. Gastric hemorrhage in cholecystitis and cholelithiasis is not uncommon, and often blurs the diagnosis. If the stomach is opened at operation, however, no lesion can be found except a hyperemic condition of the mucosa and a few erosions. Hemorrhage from the stomach in *profoundly jaundiced individuals* is not uncommon.

(5) *Various infectious diseases. Yellow fever, pneumococcus infections, septicemia, grippe* (in certain epidemics, hemorrhage from the stomach, intestine, and urinary tract is fairly frequent), *measles, smallpox*, and *scarlet fever* may all produce gastric hemorrhage. That of appendicitis (Dieulafoy's black appendicular vomit) is often so marked as to suggest the presence of a deep ulcer. When the stomach is opened, practically no lesions can be found, and at most only a few small erosions. The immediate cause of bleeding varies: erosions or superficial ulceration secondary to infectious arteritis, miliary abscesses, marked hyperemia, and sometimes alterations in the blood itself start hemorrhage.

(6) Various conditions in which the blood is profoundly altered, such as *pernicious anemia, leukemia, purpura, hemophilia, phosphorus* and *arsenic poisoning, uremia, severe icterus*, and *cholemia*.

(7) *Cardiopathies occasionally.* The rupture of a small aneurysm or of a diseased arteriole, and possibly diffuse hyperemia secondary to chronic passive congestion may play an etiological rôle.

(8) *Tabes.* This is occasionally associated with gastric hemorrhage, but this symptom is probably not essential and is the result of simple or luetic ulceration.

(9) *Essential gastrorrhagia.* This condition is becoming more and more rare with careful diagnosis. The fact that it is said to be much more common in women than in men is of interest because of the belief that gastric hemorrhage may represent vicarious menstruation. Probably, however, simple ulcer of the stomach is often mistaken for such a condition. In certain cases gastric hemorrhage appears to follow some derangement of the general or visceral nervous systems, with disturbance of the regulating influence of the neighboring organs upon the general circulation. This may perhaps explain the gastric hemorrhage of *appendicitis* and *gall-bladder disease*.

(10) *Gastric hemorrhage* in the newborn—probably of toxic or infectious origin.

Symptoms.—The symptoms depend partly on the extent of the hemorrhage and partly on the underlying cause. Sometimes those due to hemorrhage may be entirely overlooked because of the severity of the others

(cardiac and renal disease and exanthemata). The *onset* may be sudden and without prodromal symptoms, but if the underlying lesion is painful (gastric ulcer), an increase of the gastric symptoms, and a feeling of fulness, discomfort, or heat in the epigastrium, with exacerbation of pain are often noted. Sometimes bleeding, even if constant, is so slight that no gastric symptoms result, and only a progressive, often exceedingly slow, loss of strength and progressive anemia with later the usual dyspeptic symptoms of marked anemia. If hemorrhage is at all severe, it is manifested by more or less syncope, pallor, cold sweats, tinnitus aurium, giddiness, small pulse, great anxiety or fear, and sometimes by complete collapse with loss of consciousness. Any sudden, unexplained asthenia or anemia may be caused by gastric hemorrhage, sometimes without previous digestive history. This is usually due to ulceration frequently without hematemesis, especially if the ulcer is duodenal. Tarry stools often indicate the diagnosis. They may, however, continue to be passed for a day or two or even longer after the collapse.

After slight hemorrhage the condition of the blood rapidly becomes normal. If the bleeding does not stop, however, progressive secondary anemia gradually develops. After very severe hemorrhage anemia may be profound and the reduction of hemoglobin and red cells may persist some time after cessation of bleeding. Repeated hemorrhages occasionally produce changes in the blood similar to those of primary or pernicious anemia.

Vomited blood may be bright red if very abundant or associated with gastric achylia, or black like "coffee grounds" because of the action of hydrochloric acid. The latter condition is especially common when moderate bleeding results from ulceration. More than 2 liters may be vomited at one time; but if bleeding is slow or slight and the stomach is not very irritable, hemorrhage may be manifested by the passage of tarry stools. Sometimes it may not be observed for two or three days, since constipation frequently follows hemorrhage.

In many cases (a majority of ulcerative lesions) neither hematemesis nor visible melena occurs and the quantity of blood lost is too slight to color the feces. Under such circumstances only delicate chemical tests (benzidin, guaiac, etc.) demonstrate the bleeding. They are of extreme importance in the diagnosis of gastro-intestinal neoplasms which generally cause slight and not excessive bleeding and are distinguished by the persistent presence of occult blood in the feces. No examination for progressive anemia of unknown cause is complete without a careful analysis of the stools for occult blood. Bleeding from the stomach or intestine at times produces slight digestive symptoms, or none at all which would implicate the gastro-intestinal tract as the source of trouble.

Diagnosis.—The diagnosis of gastric hemorrhage is easy in cancer or ulcer of the stomach when hematemesis occurs. The sudden vomiting of blood which is often preceded by an exacerbation of the gastric symptoms is usually associated with or followed by more or less marked collapse. When hematemesis does not take place and the other symptoms are evident, a careful examination of the feces usually decides the diagnosis.

In *hemoptysis* the blood is usually red and frothy, and, as a rule, is present in the sputum for several days. This symptom is usually associated with a cough. It is not unusual, however, when hemorrhage is slight, for

the blood to be swallowed and then vomited. Under such conditions the history and the examination of the chest usually indicate the correct diagnosis. A careful examination of the nose and throat demonstrates the source of the blood in *epistaxis*. Chemical tests indicate whether the color of black or tarry stools is due to blood (melena) or to food or drugs. The presence of fresh red blood in the feces is practically always an indication that the bleeding is not of gastric origin, but occurs in the colon. Alcoholic patients with evidence of cirrhosis of the liver may have *esophageal varices* which bleed, in some cases so extensively as almost to exsanguinate the patient.

The usual cause of *gastric bleeding*, in the absence of other demonstrable causes (trauma, infection, the swallowing of poisons, etc.), is ulcer or cancer; of hematemesis, ulcer. The next most probable cause is disease of the liver (cirrhosis, Banti's disease, etc.). Unexplained hemorrhages are still occasionally ascribed to *hysteria* but probably without sufficient evidence.

Prognosis.—The prognosis depends on the severity and frequency of hemorrhage and the *underlying causes*. Gastric hemorrhage *per se* is rarely fatal.

Treatment.—The treatment consists of rest, which must be absolute when hemorrhage is severe; absolute starvation; application of an ice-bag to the stomach; and hypodermic administration of morphin. Water, or water with glucose, salt, or soda may be given by rectum, either by the Murphy drip method or repeatedly in small quantities as an enema. Usually a few bits of ice may be given by mouth. Salt infusions are useful, but in severe cases less efficacious than blood transfusions, which often seem to exert a marked hemostatic effect. Injection of 10 c.c. of horse-serum sometimes stops bleeding. Adrenalin, calcium salts, ergotin, gelatin, thromboplastin, and other drugs supposed to produce superficial coagulation specifically are singularly ineffective.

During *convalescence*, rest, gradual resumption of activities as improvement takes place, restriction first to a liquid, then to a soft non-irritating diet after the first few days of absolute starvation, fresh air and sunshine, control of the bowels, at first by enemata, hypodermic injections of iron and arsenic (cacodylate of iron, etc.), and, when improvement seems slow, transfusion of properly matched blood, are the most important therapeutic factors.

Thomas R. Brown.

PYLORIC STENOSIS IN INFANTS

In addition to the various forms of pyloric stenosis in adults there is a type which not infrequently develops in infants very shortly after birth. This is of three types: the very rare *congenital atresia* evidenced by complete constipation after the meconium is passed, the vomiting of all food, and early death; *hypertrophic stenosis* of the pylorus which may be manifest shortly after birth or sometimes not for several weeks; and *pylorospasm*, which is said to be purely functional and occurs in certain infants shortly after nursing begins. It does not cause dilatation of the stomach, and stops

spontaneously or yields to merely symptomatic treatment (gavage, careful regulation of diet, and perhaps administration of atropin) within a few weeks.

The second type produces explosive attacks of vomiting after nursing, although not always after every nursing; marked constipation; oliguria; in some cases the formation of a palpable tumor; visible peristalsis; usually some signs of gastric dilatation; and distention of the upper and contraction of the lower abdomen. *x*-Ray *diagnosis* is useful when the tumor is not palpable or is indefinite, and differentiates true stenosis from spasm. Some believe that the amount of bismuth or barium remaining in the stomach after two hours is the best indication of the need of medical or surgical therapy: "with slight delay and practically no residue at the end of two hours, medical treatment is indicated." The charcoal and carmine tests may also be useful. In true hypertrophic stenosis they are rarely positive in the stools. Some still consider this condition an intense, intractable spasm, but most observers believe that there is a real hypertrophy of the pyloric musculature as well as some intestinal change, and that the condition is probably most often congenital, occasionally inflammatory.

In the *treatment*, which is surgical, the Rammstedt operation of submucous section of the circular musculature has yielded the best results. Gastro-enterostomy and even resection have also been employed. Strict dieting and frequent gavage with careful nursing are necessary until the operation may be performed.

THOMAS R. BROWN.

DILATATION OF THE STOMACH

(*Gastrectasis*)

Two forms of dilatation of the stomach are recognized—the obstructive and the non-obstructive. The obstructive form is usually referable to some type of pyloric stenosis. The non-obstructive forms are the result of muscular atony, or, when acute, may follow extreme intemperance in eating or drinking.

Pyloric Stenosis with Secondary Gastric Dilatation.—Pyloric stenosis merits separate consideration because it gives rise to gastric dilatation and presents many therapeutic problems.

ETIOLOGY.—*Intrinsic causes:* (*a*) *Cancer*, not as a rule primarily in the pylorus, but originating on the lesser curvature and, by extension, involving the pylorus, gradually produces symptoms of obstruction and gastrectasis.

(*b*) Pyloric, juxtapyloric, and duodenal *ulcer* with stenosis and varying degrees of organic obstruction, cicatrization, perigastric adhesions, and pylorospasm (often secondary to ulcers far removed from the pylorus) also produce dilatation.

(*c*) *Other types of ulceration*—luetic, tuberculous (very rare), and that following ingestion of caustic and corrosive poison.

(*d*) Other *neoplasms* at the pylorus, such as polyps, sarcoma, hemangioma, and myoma, also play an etiological rôle.

(*e*) *Foreign bodies* of various kinds, occasionally large biliary calculi secondary to perforation of the gall-bladder into the stomach, may produce this disturbance.

(*f*) *Pyloritis*, or *pyloric hypertrophy*, due to severe visceroptosis with a constant drag of the ptosed, atonic, slowly emptying viscus upon the fixed duodenum, which produces low-grade inflammation and sometimes is associated with hypertrophy of the muscle, really produces duodenal obstruction which is symptomatically equivalent to pyloric stenosis.

(*g*) *Pylorospasm* may be due to a great variety of causes—gastric ulcer, appendicitis, renal calculus, or pyelitis, sometimes to disease of the gall-bladder and diseases of the genitalia. Occasionally it is a simple neurosis. In all these conditions, if the spasm is slight or of short duration, it produces no dilatation of the stomach, but if marked and persistent, the associated hyperperistalsis, hypomotility, and hypersecretion in time produce dilatation. In some cases this may be delayed a long time by the initial compensatory hypertrophy of the stomach wall.

Extrinsic Causes.—Among the extrinsic causes of pyloric compression are perigastric adhesions in stomach, duodenum, gall-bladder, and intestine; pancreatic carcinoma; tuberculosis or malignancy of the mesenteric glands; enlargement of the liver or gall-bladder (cirrhosis, carcinoma, etc.); and possibly marked constriction by corsets. Adhesions may produce only slight organic obstruction, but the associated spasm is so great as to cause marked symptoms of obstruction. The functional response is often far out of proportion to the severity of the organic lesion, perhaps on account of the instability and excitability of the nervous system, or the nature and situation of the organic lesion. The fact that at operation these functional manifestations may be reduced to a minimum or even completely abolished by anesthesia does not justify a denial of their existence, or a minimization of their importance in the production of symptoms, for gastric disturbances in many instances depend on such a bewildering mixture of organic and functional lesions that evaluation of the relative rôles of each is singularly difficult. In psychasthenic individuals very slight, easily overlooked organic lesions may produce remarkably severe motor, secretory, and sensory disturbances which persist for a long time after the causative lesion is cured. In apathetic subjects, on the other hand, surprisingly gross organic lesions are at times associated with very little disturbance of function.

Symptoms.—If pyloric obstruction is marked or prolonged, characteristic signs and symptoms of gastric dilatation develop. *Pain* is almost always present. Its severity depends on the degree of obstruction and the amount of food eaten. This symptom is often relieved entirely or in great part by vomiting or by gastric lavage.

A *tumor* is frequently palpable. *Vomiting* is very constant and very significant in that it often indicates the diagnosis. It usually increases in frequency and severity as the condition progresses. Often at the onset of obstruction the only symptoms are discomfort after meals, fulness, distention, pyrosis, and eructation. Later, small amounts of material are vomited at intervals of considerable length, the amount of vomitus increasing and the intervals diminishing as the obstruction becomes more complete. As long as the gastric musculature is good, vomiting may occur after each meal;

when atony develops, as it almost always does during the course of the disease, the intervals between the attacks of vomiting are prolonged. The quantity of vomitus becomes enormous (several quarts sometimes) and food, often eaten several days previously, is present. The gastric content is fermented, often very acid in the benign obstructions, putrid in the malignant stenoses, contains much thick ropy gastric mucus, lactic and butyric acids in patients with achylia (especially those due to carcinoma), and, very rarely, fragments of the growth which causes the obstruction. The interval between the ingestion of easily recognized food-stuffs (carrots, raisins, etc.) and vomiting is a valuable index of the degree of obstruction. Blood (usually coffee-ground or black) is sometimes present when the lesion is ulcerative. Acid or fetid eructation is very common between the attacks of vomiting.

The onset of *dilatation* varies greatly in different individuals. Some stomachs undergo early dilatation, while in others the first reaction is an increase in tone, or even a true compensatory hypertrophy of the musculature which is analogous to the cardiac hypertrophy of the early stages of stenotic valvular disease. The dilatation may be determined by percussion, palpatory auscultation, noting the extent of the clapotage, distention through a stomach-tube, administration of sodium bicarbonate and tartaric acid in doses sufficient to produce enough gas to render the stomach visible through the abdominal wall, and, most satisfactorily, by *x*-ray examination.

Peristalsis is often visible, although in very marked dilatation with *atony* the waves appear very infrequently. Slapping the abdomen with a cold wet towel often helps to render them visible. *Antiperistaltic waves* are sometimes seen. *Peristaltic agitation* is often more or less periodic, and is due, probably, to fatigue of the viscus.

The *x*-ray shows the degree of dilatation, and, to a certain extent, of the associated atony—instead of emptying in the normal four to six hours, the stomach may retain its contents for many hours, in some cases for several days before it is emptied.

The *fasting stomach* shows macroscopical and microscopical evidences of food retention, the *extent* depending on the degree of obstruction. In the early stages only microscopical evidences of retention are found after twelve hours. Marked macroscopical retention after this interval is almost always an index of organic obstruction, although it may occur in high-grade atonic dilatation of myogenic origin. Microscopical examination of the stomach contents reveals yeast, food, mucus, leukocytes, blood-cells, and occasionally tumor cells; sarcinæ may be present in obstruction with hypersecretion; and Oppler-Boas bacilli are often found with occasional infusoria in obstruction (usually malignant) with achylia. The odor of the gastric contents may be acid, musty, or putrid. If the material is allowed to settle, it often separates into the characteristic three layers. The changes observed after the *test-meal* (always preceded by a gastric lavage) are less important. *Hypersecretion* is evidence of *benign stenosis*. *Achylia* is common in carcinoma, and is associated with the presence of lactic and butyric acids as a rule.

The *general condition* of the patient is always poor. The *appetite*, though often small, is sometimes good or even excessive, but the fear that food may increase discomfort (*sitophobia*) results in marked reduction of the food intake. There is *loss of weight and strength*. The urine is concen-

trated, scant, and often contains few chlorids. *Constipation* is the rule. *Anemia* sometimes develops, but is very difficult to recognize from the condition of the blood on account of general desiccation (oligemia); it is usually marked in malignant obstruction; and not uncommon in that resulting from benign ulceration. In the latter condition, the associated emaciation caused by starvation may produce cachexia quite impossible to differentiate from that of malignancy. *Gastric tetany* occasionally develops in gastrectasy, usually because of pyloric ulceration with marked obstruction and hypersecretion, and marked loss of hydrochloric acid by vomiting. The nature of the condition is not definitely understood. It may possibly result from disturbance of the function of the parathyroid gland and of the calcium metabolism.

Diagnosis.—The diagnosis can usually be made easily from the history, abdominal inspection, examination of the fasting stomach contents, the *x*-ray findings, and the symptoms. In *atonic dilatation* often associated with ptosis, the dilatation usually is less, and the fasting stomach retains, as a rule, little microscopic food. Duodenal stenosis is comparatively common, and the symptoms are practically identical, the therapeutic indications practically the same. Occasionally it is difficult to differentiate the gastrectasis due to pyloric stenosis from the partial type associated with bilocular *hour-glass* deformation of the stomach (*mediogastric stenosis*). Very careful and repeated studies of the gastric contents may suggest the condition, but, as a rule, it is only by means of *x*-ray studies that a definite diagnosis can be made.

The nature of the *stenosis* is usually determined by a careful study of the case, the increase, decrease, or absence of free hydrochloric acid in the gastric contents, examination of the stools for occult blood, the presence or absence of luetic stigmata, the results of the Wassermann test, the evidence of gall-bladder, pancreatic, or tubercular diseases, and careful radiographic and fluoroscopic examinations.

Treatment.—The treatment obviously depends largely upon the nature of the stenosis. Administration of soft liquid foods, rest after meals, frequent gastric lavage, injection of fluid by rectum (water with glucose and salt or soda) by the Murphy drip or as small repeated enemata give comfort and symptomatic relief. Since, however, the condition is usually due to mechanical obstruction, the treatment must be fundamentally surgical. Separation of adhesions, resection, pyloroplasty, and gastro-enterostomy are suitable therapeutic measures. While pyloroplasty or resection are the most desirable operations for carcinoma and deep ulceration with extensive adhesions, technical difficulties or the condition of the patient often prevent them, and posterior gastro-enterostomy must be substituted. It is in pyloric obstruction with dilatation that gastro-enterostomy produces the most brilliant results, for in most of such cases, even with malignancy, the leading symptoms result from mechanical obstruction and the consequent inevitable starvation. The relief of this obstruction by the formation of a new free opening and the resulting ability to take a normal amount of food leads to remarkable improvement. A temporary large gain in weight is not unusual even when the lesion is malignant; and there is an undoubted retardation in the progress of the disease. Jejunal or marginal ulceration may follow gastro-enterostomy in between 2 to 10 per cent. of cases. Intestinal indigestion is a frequent sequela.

Atonic Dilatation of the Stomach.—Dilatation of the stomach secondary to atony is usually less marked than that secondary to pyloric stenosis, although the two are sometimes difficult to differentiate.

Etiology.—Gastric atony is most often congenital (congenital myasthenia) and is usually associated with visceroptosis. It is more frequent in women than in men. The condition also results from strain imposed upon the stomach by overfeeding, excessive ingestion of fluid and lack of exercise, without a congenital element; during or after wasting diseases of various kinds (typhoid fever, tuberculosis, etc.); from gastritis; ulcer with hypersecretion; carcinoma of the stomach; gradual weakening of the stomach musculature by disease; persistent undernutrition which is common in women obsessed with the fear of being too fat; and from continued mental strain, excessive worry, and psychasthenia, all of which produce psychogenic or neurogenic atony, and, if persistent, atonic dilatation. All degrees of atony may be found, from the simple type without demonstrable dilatation to very high-grade gastrectasis. As a rule, however, the dilatation is not very marked.

Symptoms.—The symptoms may be practically *nil* in the milder form. In the more severe types, distention, marked clapotage often below the umbilical level in the prone position, and an increased area of gastric resonance on percussion are noticeable. Distention with air through the stomach-tube or the administration of sodium bicarbonate and tartaric acid shows that much more than the usual amount can be given before discomfort supervenes (about 700 c.c. in the normal stomach, often 1000 c.c., sometimes 1200 c.c. or more in case of atonic dilatation). The stomach empties slowly and there is sometimes seven- or eight-hour, rarely twelve-hour, retention. Examination of the stomach contents after the test-meal usually reveals, except in cases associated with ulcer, a subacidity and often achylia. The *x*-ray demonstrates a lack of tone and increased capacity, with very slight or no peristaltic contraction. Digestion is slow; there is fulness, discomfort, a sensation of epigastric weight, eructation, and persistent taste of food many hours after eating. The patient is often more comfortable on the back or the right side. Constipation is usual. At times enormous quantities of material are vomited, especially but not exclusively by patients with marked visceroptosis. This may, however, result not from *simple atonic dilatation*, but from true organic *pyloric* or *duodenal* stenosis produced by traction of the distended viscus.

Diagnosis is, as a rule, easy in the more marked cases. It is sometimes difficult, however, to differentiate *atonic dilatation* from *mild stenosis*, especially that due to persistent pylorospasm. Enormous dilatation may also be due exclusively to marked atrophy of the musculature, which can be distinguished from true *organic pyloric stenosis* only at operation or autopsy. The *x*-ray, especially the fluoroscope, percussion of the abdomen, distention of the stomach with gas or air, and the aspiration of the stomach contents six hours or more after a meal usually permit diagnosis.

Treatment must, first of all, prevent, in so far as possible, the development of atony. Insistence upon the proper amount of rest and exercise, careful regulation of the diet, massage, and setting-up exercises reduce the tendency to overdistention and increase muscle tone, and are, therefore, necessary in individuals congenitally predisposed and subject to viscerop-

sis. Great care should be exercised throughout the convalescence from long febrile or wasting diseases such as typhoid fever.

When dilatation has already taken place it is essential, first, to improve musculature by massage, selected exercises, and administration of strychnin in increasing doses; and second, to facilitate emptying of the stomach. Small concentrated meals, often six instead of three daily, should be given, and excess calories. Very coarse, greasy, or soggy foods must be avoided and, at first, all food taken in purée form. The fluid intake with meals should be small, "no fluids with solids, no solids with fluids." The establishment of careful habits of eating, and sometimes the temporary wearing of an abdominal support when the patient is in the upright position are helpful. Lying on the right side after meals may prevent dilatation, but in the more marked cases a rest cure with massage, hypodermic injection of arsenic, and in the very severe cases gavage—usually in the morning before the first meal, or late in the evening some time after the last meal—are desirable. Surgical therapy for simple atonic dilatation without organic pyloric obstruction is very disappointing. Gastro-enterostomy is the operation most employed and is usually unsatisfactory.

Acute Dilatation of the Stomach (*Acute Gastric Paralysis*).—Etiology.—Acute gastric dilatation is a very serious condition which is most frequently seen after *operations*. Although it usually follows abdominal operations, it occasionally develops after simple extra-abdominal surgery such as perineoplasty. This suggests that in certain cases at least the *anesthetic* (ether, chloroform, etc.) may be an etiological factor. This type of dilatation may result from abdominal *injury*, injuries elsewhere in the body, and from severe *nervous shock*. It also occurs in certain *infectious diseases* (typhoid fever, pneumonia, and scarlet fever).

One of two mechanisms probably produces the condition: either a marked inhibition of the vagus or overstimulation of the sympathetic as the result presumably of trauma, peritonitis, etc.; or twisting, kinking, or strangulation of the duodenum (arteriomesenteric ileus), which with a dilated duodenum is frequently demonstrated at operation or autopsy.

Symptoms.—The symptoms are very striking, and the onset usually sudden. Profound prostration; vomiting of large amounts of fluid, but not, as a rule, of fecal material; marked distention of the abdomen; peritonitic facies; small, thready pulse; and other symptoms of collapse are characteristic. The localized distention and the lack of fecal vomiting help to differentiate the condition from intestinal obstruction.

Prognosis.—The prognosis is bad; 74 of Conner's 102 patients died.

Treatment.—Very frequent lavage of the stomach, application of an ice-bag to the abdomen, hypodermic injections of stimuli, and change of position (lying on the stomach, right side, or in the knee-breast position) sometimes bring relief and even cure. Usually treatment is not successful.

Thomas R. Brown.

Diseases of the Intestines

DIARRHEA IN INFANCY AND CHILDHOOD

Definition.—Diarrhea is a symptom, not a disease. The term includes all conditions in which there are frequent loose evacuations of the bowels, and is associated with an increase in the quantity of intestinal secretion and peristalsis.

Incidence.—Infants and children are particularly susceptible to diarrhea. The condition is most frequently seen in the hot summer months, especially July and August; the incidence and death rate are seemingly in proportion to the increase in temperature during this time.

Etiology.—Poverty, poor hygiene, crowding, uncleanliness, rickets, and malnutrition are all predisposing factors. Diarrhea is four times as frequent in artificially fed as in breast-fed infants. In many instances it is due to contamination of the milk-supply with bacteria. With the advent of certification of milk and pasteurization, the death rate from the diarrheal diseases has fallen. Attempts which have been made to discover the relationship between milk with a high bacterial content and the incidence of diarrhea seem to demonstrate that it is not the multiplicity of bacteria but their pathogenicity which is of importance in the etiology of the disease.

Bacteriology.—In a study of the bacterial flora of the intestines of healthy breast-fed infants Kendall has shown that members of the *Bacillus lactis aërogenes* group are found most commonly in the upper intestines, of the *colon* group at the ileocecal valve and cecum, while the *Bacillus bifidus* and similar organisms dominate the large intestine to the sigmoid flexure.

Escherich drew attention to the difference between the intestinal flora of the artificially fed and breast-fed infant. Kendall believes that the difference in the intestinal flora in infancy and later life probably depends to a great extent upon the character of the food ingested. The complexity of the normal picture has made it difficult to interpret the bacteriological findings in the diarrheal diseases of childhood, and, as a consequence, no convincing data are available. The relation of bacterial infection to intestinal indigestion is not yet proved, but there seems to be little doubt that bacteria have a causative relation to dysentery.

The most carefully studied bacteria concerned with infantile diarrhea are those which fall in the group of dysentery bacilli. The Shiga type isolated during the great epidemic of 1897 and 1898 in Japan, and the Flexner type isolated in 1900 in the Philippines, as well as those studied by Hiss and Russell, and Park and Dunham, in New York, have all been found to exist in this country. It is possible to differentiate them by differences in their effect on carbohydrates. In the United States, infection with the Flexner type is somewhat more common than with the Shiga type, especially along the Atlantic seaboard.

The dysentery bacillus is not found, as a rule, in the blood-stream. At least three instances have been cited, however, in which it was present in the blood; and others are reported in which pure cultures were obtained after death from the mesenteric lymph-nodes. Although the causal connection between the dysentery bacillus and the diarrheal disturbances of children has not been finally established, there is strong presumptive evidence that, in isolated cases, it is the offending organism.

The importance of other organisms, especially the *Streptococcus*, must not be overlooked. There is considerable evidence that members of this group may produce destructive lesions in the intestine following infection by members of the dysentery group.

Morbid Anatomy.—The lesions are varied and are generally restricted to the large intestine and the last 3 or 4 feet of the small intestine. In mild cases there may be only superficial catarrhal inflammation of the gastro-intestinal tract, while in severe cases characteristic lesions may be lacking. There may be redness and swelling of the solitary follicles and Peyer's patches. The submucosa is generally infiltrated with serum and small round cells. In severe cases, ulcers often develop and sometimes a pseudo-membrane forms. There is usually hyperplasia of the mesenteric lymph-nodes. The changes in other organs are not characteristic. Otitis media, bronchopneumonia, and pyelitis are common complications. The liver is often enlarged and fatty, and the spleen slightly enlarged. There may be some degeneration of the kidney. The brain is rarely affected.

Clinical Types.—Diarrhea Due to Infection in Other Parts of the Body (*parenteral infection, toxic diarrhea*).—The symptom diarrhea is often so pronounced as to divert attention from other parts of the body where the primary cause of the disease is to be found. Diarrhea may be a prominent symptom of colds, otitis media, mastoiditis, pneumonia, and pyelitis, and is not infrequently seen in the exanthema during the eruptive stage. A careful physical examination usually reveals the cause of the diarrhea when it lies outside of the gastro-intestinal canal.

Diarrhea from Mechanical Irritation.—Diarrhea is less often caused by mechanical irritation in infants than in older children. Scybal-lous stools may be associated with alternating constipation and diarrhea. Ingestion of foreign bodies, such as sea sand and dirt, may result in diarrhea. On examination of the stools the offending agent can usually be found.

Diarrhea Due to Improper Food.—Improper food causes diarrhea most often in infants. Overfeeding with sugar or fat frequently results in numerous loose stools. Starch indigestion, which is relatively rare, is also associated with mild diarrhea. The stools are very acid and irritating, and scald the delicate skin of the buttocks.

Acute intestinal indigestion occurs in patients of all ages and is due to unsuitable food. Hot summer weather is a predisposing factor, or, occasionally, a sudden fall in temperature after continued hot weather. This is not uncommon in Boston when a sudden drop in the temperature of 20 or 30 degrees is caused by the east wind which blows in from the sea. In older children unripe or over-ripe fruits often seem to cause an attack. The onset is usually abrupt and is characterized by nausea and vomiting, followed quickly by colicky pains, distention, restlessness, fever, and diarrhea. The stools may be few in number, or as many as fifteen may be passed in twenty-four hours. They usually smell foul at first, then are liquid, and contain mucus and more or less undigested material. Blood is not present unless the symptoms persist for several days. When properly treated such a disturbance is usually short; but if treatment is delayed more serious conditions may develop. Dehydration and acidosis are serious complications. Usually, however, the attacks are short. There is a tendency to recurrence, especially if the weather remains hot and the environment is not changed.

The diagnosis depends upon the short duration of the diarrhea, the absence of toxic symptoms, and the presence of blood in the stools.

Chronic intestinal indigestion (*fermentative diarrhea, intestinal intoxication*) cannot at first be sharply differentiated from the acute type. It may be superimposed on it or may develop suddenly with vomiting, restlessness, distress, and fever, the temperature rising sometimes as high as 106° F., and rarely being below 102° F. Nervous symptoms are usually prominent and there may even be convulsions. The child may be irritable and sleep poorly, or may lie in a dull stupor with sunken eyes and a weak pulse. Increasing drowsiness, which changes to coma, is occasionally noted. Vomiting may be a prominent and persistent symptom and is always accompanied by great thirst. When vomiting and diarrhea occur simultaneously the body tissues become rapidly dried and the child looks very sick. If the dehydration is marked, the eyes become sunken, the expression anxious, the skin loses its normal vigor, and the circulation becomes weak. There may be either constipation or diarrhea at the onset. If constipation is an early symptom, diagnosis is often impossible until the diarrhea begins. At the onset the stools are usually very frequent, offensive, and accompanied by gas; sometimes as many as eighteen are passed in twenty-four hours. Before the expulsion of gas the infant apparently suffers from colicky pains. Later in the disease the gas and foul odor are usually not present, the stools diminish in number, and mucus and pus of a characteristic odor appear. After the bowels are emptied with a cathartic the temperature usually falls and the child may proceed to convalescence. In other instances, the temperature does not fall, the diarrhea persists, and complications, such as bronchopneumonia, otitis media, or pyelitis, may develop. Chronic intestinal indigestion usually causes great wasting, and if efforts are not made to maintain the body fluids, the tissues become dehydrated. This intensifies all the symptoms and predisposes to an unfavorable outcome. The loss of fluid from the body is almost always so great that the urine becomes scanty and concentrated and may contain a small amount of albumin and a few casts.

If all milk has been removed from the diet, the addition of cow's milk to the food, even in very small amounts, is sometimes followed by a severe relapse, even after the temperature has returned to normal. This rarely happens if human milk is given.

Infectious diarrhea (*ileocolitis, enterocolitis*) differs clinically from the conditions already described in that it is often more severe and is nearly always associated with the presence of blood, pus, and mucus in the stools. The dividing line between severe intestinal indigestion and infectious diarrhea cannot, however, be clearly defined. There is considerable evidence that both are due to infection of the alimentary canal, most frequently by the typhoid, paratyphoid, or dysentery bacillus, and the streptococcus. Cultures of the stools have demonstrated the presence of large numbers of dysentery bacilli in some cases, and of the *Streptococcus pyogènes* in others. The former organism has even been isolated from the blood-stream during life. The symptoms, aside from the presence of blood in the stools, are very similar to, if not identical with, those of intestinal indigestion.

Cholera infantum usually develops very quickly in children who were previously well, and may progress so rapidly that death results in a few hours. Fortunately, typical cases are rare. The disease begins with

vomiting, which is incessant whether or not food or liquid is given. Diarrhea may begin at the same time or a little later and is characterized by profuse watery stools which at first contain fecal material. These soon assume the appearance of rice water, and later become tinged with yellow by serum. At first the stools may be acid and scald the buttocks; when they become serous they are alkaline. The temperature is usually high, although the extremities of the body may feel clammy and cold.

Most of the symptoms may be attributed to the tremendous loss of liquid from the body. The fontanel becomes depressed, the eyes and abdomen sunken, and the skin dry. The facial expression is anxious and the complexion pale. There is marked prostration. As the blood volume decreases, the pulse becomes rapid and weak. The restlessness and great thirst which develop at first are later replaced by listlessness, stupor, and even coma or convulsions. Although no cause has yet been found for this condition, the syndrome is that of an acute bacterial infection.

Complications.—The most important complications of severe diarrhea, no matter what the cause, are acidosis and dehydration. They are often closely related and the success of treatment depends upon their recognition and correction. These symptoms occur to a greater or less degree in all types of severe diarrhea and, consequently, deserve special consideration.

Acidosis.—The most common and serious symptom of the severe diarrhea of infancy and childhood is acidosis. The younger the patient, the more quickly does it develop. It may be due to the starvation caused by prolonged vomiting, or result from loss of the fixed bases of the body in the diarrheal stools. The condition is intensified by dehydration and the consequent concentration of the normal or abnormal acids in the body. When the alkali reserve becomes diminished, there is a compensatory increase in the pulmonary ventilation in order to eliminate the carbonic acid more rapidly. This may be imperceptible at first, but as it becomes more pronounced the "air hunger" type of respiration develops. The lips instead of being cyanotic, as might be expected, have a cherry-red color. When acidosis is marked, the outlook is serious. If the carbon-dioxid combining power of the blood falls below 20, the patient rarely recovers.

Dehydration, which is just as important as acidosis, results from the great loss of body fluids in the diarrheal stools. It is recognized clinically by loss of vigor, the doughy consistency of the skin, the dry and often beefy red tongue, sunken eyes, and, during infancy, the depressed fontanel. It is difficult to combat if the patient is vomiting. If vomiting and diarrhea are concomitant, the water intake is abnormally low and the output in the stools abnormally great. In a few instances in which the fluid loss has been measured in infants with severe diarrhea, the stools have contained one quart or more of liquid.

Diagnosis.—The first step in diagnosis is to determine whether the diarrhea is due primarily to disease in the intestinal canal or to disease elsewhere. This may be done by a careful physical examination which rules out disease in other parts of the body. The respiratory diseases, and otitis media, pyelitis, and the exanthemata are, however, frequently overlooked. Occasionally tuberculosis of the mesenteric lymph-nodes or intestines may cause confusion, but the sudden onset of diarrheal diseases usually eliminates the possibility of this.

When large amounts of blood appear in the stools *intussusception* must

always be considered. Both this and diarrhea may have a sudden onset. Intussusception, however, is accompanied by the presence of a sausage-shaped tumor in the abdomen, and the passage of stools which are composed mainly of blood, while in the diarrheal diseases the admixture of pus, mucus, and fecal matter give a characteristic picture. If there is doubt, a rectal examination may be made, but this is rarely necessary because in the diarrheal diseases the abdomen becomes sunken and easily palpated.

Nervous symptoms at the onset are sometimes suggestive of *meningitis*. During infancy the level of the fontanel usually provides decisive evidence: in meningitis it is usually elevated and bulging; and in diarrhea, sunken, especially if the stools are frequent and profuse. If doubt persists after the body fluids have been brought back to normal, a lumbar puncture will decide the diagnosis.

The diagnosis depends in a large part upon the history. Often intestinal indigestion cannot be distinguished from dysentery, and at times, although the onset is typical of the former, the disease eventually assumes the characteristics of the latter. If blood appears in the stools, the disease is usually dysentery, but occasionally patients with mild dysentery do not pass bloody stools. Cholera infantum, on the other hand, cannot be confused with any other condition and is characterized by the profuse rice-water stools.

Prognosis.—The prognosis depends upon the social and hygienic surroundings, whether the child has been artificially or breast fed, the season of the year, and the treatment. The milder forms of diarrhea are rarely fatal except in poorly nourished children. The prognosis is serious when such complications as prolonged fever and acidosis develop. Of greatest importance in the prognosis are the prevention of desiccation of the body and the recognition and treatment of acidosis. Cholera infantum has a bad prognosis and is fatal unless desiccation and acidosis can be prevented. These two complications always diminish the chances of recovery.

Treatment.—The intestinal disorders of infancy and childhood are preventable. Many of the larger cities in this country have materially reduced the incidence and mortality of the diarrheal diseases during the last decade by improving the milk supplies, pasteurization of milk, and health education. Propaganda for breast feeding has played its part. Improvement of living conditions and fresh air funds have done much for city children. A better understanding of the cause of rickets and improved treatment is also lowering the incidence of this disease and the accompanying malnutrition, both of which predispose to the diarrheal diseases.

Abundance of fresh air and sunlight should be sought. During hot weather, babies ought to sleep out of doors both day and night. The clothing should be light and adjusted to changes of temperature. The body may be sponged off two or three times a day during the intense heat. Since the quantity of perspiration is increased during hot weather, more liquids should be given than on cold days. As an infant cannot express his wants and may be thirsty without being able to say so, water to drink should be offered many times a day.

Great cleanliness should be insisted upon, and flies kept away from the infant and its food. If the infant is artificially fed, only pasteurized or sterilized milk should be used.

At the *onset* of diarrhea the bowels should be cleared with castor oil or

with 1 grain of calomel in divided doses if there is any distention or evidence of retention of toxic fecal material. If, on the other hand, the abdomen is flat or sunken and there is no evidence of fecal retention, cathartics should not be given, and colonic irrigations of normal salt solution are of value. (Two or three quarts can be used even in a small infant.) This cleanses the bowels, removes the toxins, and supplies liquid for absorption if any is retained. The irrigation may be given with a fountain syringe, and a No. 25 French catheter is passed as high as possible into the rectum, with the patient lying on his back with the hips elevated. The fluid should be allowed to run in slowly from the bag, which is hung not more than 2 feet above the level of the patient, until about a pint has been introduced or until the abdomen becomes distended. It should then be allowed to run out. This procedure should be repeated until the discharged water is clear. Such treatment may be given every six to twelve hours unless it depresses or disturbs the patient.

Since there may be a great *loss of water* from the body, it is very important to measure and record the fluid intake. Under ordinary circumstances most infants take a total of 3 pints of liquid in twenty-four hours. To this must be added the 1 or 2 pints lost in the watery stools. It is usually necessary for the fluid intake to be 4 pints or more during severe diarrhea. Three quarts are frequently required; and occasionally it may be necessary to introduce as much as 5 quarts before the body fluids are restored to normal. If the requisite amount of water cannot be introduced by mouth or rectum, it must be administered subcutaneously, intraperitoneally, or even intravenously in the form of normal saline solution. If this is done early in the disease and the fluid content of the body kept normal, surprising and brilliant improvement usually results and the more serious symptoms are averted. In some cases, however, no matter how much fluid is introduced desiccation progresses and death results. Nevertheless, dehydration should always be counteracted if possible. There is rarely any indication for transfusion.

The necessity for intravenous administration of liquid usually comes after a period of starvation and, consequently, 10 per cent. glucose may be added to the saline. This sometimes causes severe reactions which are probably due to improperly prepared and sterilized solutions. The glucose should be chemically pure and sterilized immediately before using.

Acidosis is at times superimposed on anhydremia, and if accompanied by "air hunger" and cherry red coloration of the lips, usually requires immediate treatment. Bicarbonate of soda may be given by mouth until the urine becomes alkaline. Sometimes very large quantities are tolerated, but during infancy it is usually unwise to give more than 3 drams in two days because of the possibility of converting an acidosis into an alkalosis or tetany by overdosage. It may also be administered intravenously as recommended by Howland and Marriott. If given subcutaneously, the bicarbonate and not the carbonate must be used, for the carbonate is irritating and causes sloughing around the site of injection. The sodium bicarbonate solution should be sterilized under pressure; boiling in an open vessel may convert enough into sodium carbonate to be harmful.

Drugs.—Bismuth has proved to be the most serviceable of the intestinal astringents and antiseptics. The subnitrate should not be used because of the possibility that it may be broken down by bacterial action

into harmful compounds. The subgallate and subcarbonate of bismuth (in doses of 5 to 10 grains every hour until the stools become discolored) have proved satisfactory. They rarely upset the stomach.

Opium in the form of paregoric may be very useful or very harmful. It is contraindicated when the intestines contain fecal material, gas, or toxic substances. Under such conditions, if given in sufficient amounts to retard or stop peristalsis, all the symptoms may be intensified. If, on the other hand, the bowels are completely cleared and there is no evidence of absorption, it may be of great value in stopping the diarrhea and preventing further loss of fluid from the body. It is of special value in cholera infantum. One to three minims of paregoric are usually administered after each movement of the bowels. As the number of stools diminishes, the dosage is automatically decreased. In the most severe cases morphin may be given hypodermically, but it should always be remembered that relatively smaller doses should be given to infants than to adults.

The ordinary stimulants, such as strychnin, alcohol, camphor, and caffein, are of little or no value and may be harmful. If sufficient fluid can be introduced into the body they are rarely required.

Diet.—The importance of the diet in diarrhea is second only to that of the fluid intake. There are two distinct methods of treatment: one is to stop milk and substitute water, cereals, and sugar; the other to administer protein milk, buttermilk, or boiled skimmed milk with high protein and low sugar and salt content. A conservative method is to withdraw all milk for twenty-four to forty-eight hours until the bowels are completely cleared out. During this time care should be taken to introduce at least 2 pints or, better still, 4 or more pints of liquid into the body. Fat is poorly digested during diarrhea, probably because the mesenteric glands through which it is absorbed are affected. It should, therefore, be omitted from the diet. Boiled skimmed milk, buttermilk, or protein milk may then be given, 1 to 2 ounces every four hours. When these forms of milk are used it is better not to add sugar to the mixtures until the stools become formed. Thick cereal gruels may be added early in order to supply sugar. There is considerable evidence that in infants and young children the glycogen supply of the body is depleted by twenty-four hours of fasting. After the vomiting has stopped and the bowels are cleared, milk in some form may be carefully added to the diet.

Overfeeding should be avoided during convalescence, as it may result in a relapse which is usually more difficult to cure than the original attack. Improper selection of either diet or medication may do considerable harm. Removal to the cooler air of the country, as soon as it is safe, is beneficial in the treatment of diarrhea. An infant should not be clothed so heavily that it perspires, but should be kept comfortably warm with the abdomen covered continuously with a light woolen band. Each case is a law unto itself and treatment must be determined according to the symptoms. The one symptom which is common to all cases and which must be corrected, no matter what else is done, is desiccation. Unless this is treated by every available means, other methods of treatment will be ineffectual. Finally, the symptoms of acidosis must be watched for and properly treated.

Serum Therapy.—Up to the present time no satisfactory serum specific has been made available for the treatment of these infections.

Fritz B. Talbot.

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DIARRHEA IN ADULT LIFE

Definition.—Diarrhea is, pathologically, frequent evacuation of the intestines, and generally follows irritation or inflammation of the mucous membrane. It may be either acute or chronic. A large part of the intestinal tract is usually involved, but special diagnostic aids, such as the *x*-ray and the proctoscope, often demonstrate localized lesions. As diarrhea is merely a symptom of disease, it is important to study all cases from the standpoints of pathology and infection.

Etiology.—The chief causes are exudation of serous fluid into the bowel and increased peristalsis; the first is probably primary and of more importance than the latter. The other causes are so very numerous that, although they have never been satisfactorily classified, the following outline may be helpful:

Ingesta.—Overfrequent or overabundant eating or drinking is not only harmful in itself, but is apt to lead to the ingestion of deleterious substances or organisms. Foods which decompose readily, such as unripe or overripe fruit, ice-cream, and sea-foods, and also water may carry grave infection. Indeed, infected water is the most common source of such serious diseases as dysentery, cholera, typhoid fever, and paratyphoid fever. In the tropics, and sometimes also in temperate climates, dysentery is due to the water-borne *Entameba histolytica;* in temperate zones, however, the *Shiga bacillus* is the more usual cause of acute epidemic dysentery. Various other protozoa, such as Trichomonas, Giardia (lamblia), and Cercomonas, are common causes not only in the tropics, but occasionally also in other regions, such as the United States. These are conveyed by food. In certain cases of meat poisoning the *Bacillus enteritidis (Gärtner's bacillus)* is the cause. Poisons, such as arsenic, mercury, silver salts, and various cathartic medicines, often provoke diarrhea. Some individuals have diarrhea after the ingestion of certain foods (shell-fish, strawberries, eggs), probably because they are hypersensitive.

General Toxic Conditions.—The general toxic conditions which play an etiological rôle include sepsis, measles, toxic goiter, Addison's disease, pneumonia, cancer, and Bright's disease. Angioneurotic edema, certain forms of purpura, and also pellagra and sprue are probably included in this group.

Secondary Circulatory Disturbances.—Circulatory disturbances secondary to chronic heart disease, adhesive mediastinopericarditis, cirrhosis of the liver, and chronic productive inflammation of the lungs may induce diarrhea by producing chronic passive congestion.

Psychic Disturbances.—Fright, emotional disturbances, hysteria, and chronic fatigue may induce diarrhea in nervous individuals.

Organic disease of the gastro-intestinal tract is a frequent cause of diarrhea, usually of the chronic type. The following classification of such etiological conditions has been made by Bettmann:

Organic disease above the colon: Gastrogenic, pancreogenetic, enterogenetic.

Organic disease of the colon: Catarrh, ulceration, coprostasis, tuberculosis, protozoic changes, conditions produced by carcinoma, sarcoma, polyps, or syphilis.

The most common form of gastrogenic diarrhea results from the absence of gastric secretion (achylia gastrica, atrophic gastritis) or insufficient secretion (hypochylia). Destructive diseases of the pancreas, which are usually malignant, may also produce diarrhea. Chronic catarrh of the small intestine and defective digestion which results in fermentation or putrefaction are other causes. The various diseases of the colon mentioned above may or may not be accompanied by diarrhea.

Symptoms.—Diarrhea is either acute or chronic according to the etiological factors and the resulting pathological changes.

Simple acute diarrhea, ordinarily due to ingestion of infected drink or food or unripe fruit, is characterized by frequent evacuation of material which is at first solid or soft, but soon becomes chiefly fluid. Colicky pain is usual, and if the rectum becomes involved, tenesmus accompanies the movements. Moderate tympanitis with borborygmus is usual. There may be vomiting in the very acute attacks, followed by loss of appetite, thirst, and coating of the tongue, which may become dry. Fever is usually absent, although the temperature may be elevated one or two degrees and occasionally rises to 104° F. or more in young patients. Collapse sometimes follows in very severe cases when large quantities of fluid are lost and colic is severe. The stools number from four or five to twenty or more per day and vary in character. They are usually thin and watery, light brown or gray in color, and often have a foul odor. They contain flakes or masses of mucus, and undigested food may be seen early in the attack. Blood is unusual, but may be present in very severe attacks.

Chronic diarrhea may follow the acute form or result from passive congestion secondary to obstruction of the portal circulation. It is, however, more frequently due to insufficiency or absence of hydrochloric acid in the gastric secretion (achylia gastrica), protozoan infection, or organic disease of the colon or rectum, especially cancer, syphilis, and tuberculosis. The stools number three to six or more daily, usually contain mucus in considerable quantities, and blood and pus when ulceration has occurred. Severe pain is unusual, but mild griping and discomfort in the abdomen with rumbling and distention are frequent. When the rectum is involved tenesmus is often distressing. Several loose movements before and after breakfast (morning diarrhea) are rather typical of the diarrhea associated with insufficient gastric secretion. When due to organic disease the nutrition of the patient is impaired and anemia develops. With ulceration, perforation may occur and cause general or local peritonitis, sometimes with the formation of an abscess.

Diagnosis.—In acute diarrhea it is well to keep in mind the possibility of a specific bacterial or protozoan infection. Marked distention and

rigidity of the abdominal muscles should excite suspicion of inflammation of the peritoneum. As leukocytosis does not accompany simple acute diarrhea it should suggest the existence of more serious affections.

A history of *chronic diarrhea* demands exhaustive investigation of the gastro-intestinal tract. This should include examination of the stomach contents, proctoscopy and sigmoidoscopy, and *x*-ray studies after ingestion of an opaque meal and an opaque enema. The stools should also be examined for pus, blood, mucus, shreds of tissue, ova, and parasites; and their bacterial flora studied. It is necessary to determine the nature and the location of the lesion of which diarrhea is only a symptom. Eosinophilia suggest protozoic infection.

Prognosis.—When treatment is begun at the onset, simple acute diarrhea is usually controlled within forty-eight hours. If untreated, it may last for several days and occasionally lapse into the chronic form. Diarrhea from chronic passive congestion is a serious complication and often hastens death. Chronic diarrhea is always serious. The prognosis depends on the etiology. When it is caused by intestinal parasites it can usually be cured, but chronic amebic dysentery is prone to relapse and often resistant to cure. If due to general toxic conditions or to organic affections of the bowel, the outcome depends upon the possibility of relieving the underlying cause.

Treatment.—In *simple acute diarrhea* the irritating substance must be removed from the bowels and local rest permitted. When there is no nausea, 1 ounce of castor oil should be administered at once. The patient should be kept in bed and given no food for the first twenty-four hours. Cracked ice and hot water or weak tea may be given, but all iced drinks must be avoided. Cereal gruels, toast, and soups containing no condiments may be taken later. Milk is undesirable. Hot, preferably moist, applications (hot towels or stupes) are useful for allaying pain. When vomiting accompanies the onset, castor oil will not be retained, and the best method of ridding the bowels of the offending material is to irrigate the colon with a solution of normal saline or 1 per cent. bicarbonate of soda, warmed to 90 degrees. Calomel is a time-honored remedy, but is best avoided, as it acts chiefly by increasing the irritation and inflammation and therefore prolongs the attack.

When the pain is very severe or prostration is evident, opium should be administered at the outset (morphin sulphate, gr. $\frac{1}{8}$ to $\frac{1}{4}$, hypodermically). In less severe cases opiates should be avoided until the bowels have been emptied. Paregoric (1 dram in hot water) or powdered opium (gr. $\frac{1}{2}$ to 1), with or without bismuth subnitrate (gr. x to xx), should then be given every hour or two until the diarrhea ceases. Opium suppositories are sometimes useful. Bismuth or some intestinal astringent should be continued for several days. The constipation which usually follows diarrhea should be relieved by enemas and not by cathartics. It is most important to maintain a simple bland diet for at least one week. All foods must be thoroughly cooked and finely divided, meats being chopped or minced and coarse vegetables puréed. High seasoning, game, and iced drinks are undesirable.

The treatment of *chronic diarrhea* depends on the cause. Whatever the etiology, it is seldom cured without rest in bed, often prolonged, and a proper diet. As the patients are usually thin and anemic, the diet should have a high caloric content. Supplementary feedings are required. The dietary

outline in the section on Colitis will be found helpful, although it must be modified to suit individual tastes and defects in digestion. Application of hot moist dressings to the abdomen after meals gives comfort and is helpful. Fresh air, sunlight, ultraviolet rays, and appropriate tonics (iron, arsenic) are all useful adjuvants.

Local treatment of the colon by high enemas or irrigations is very helpful. Ichthyol (1 dram to the quart), potassium permanganate (1 part in 10,000 gradually increased to 1 part in 3000), saturated solution of boric acid, and normal salt solution are among the best preparations for this purpose. Subnitrate of bismuth (gr. xxx) and occasionally opium may be prescribed with benefit.

For *protozoic infections* the appropriate drug should be administered (see section on Intestinal Parasites). The *neoplastic conditions* require surgery or, in advanced cases, radiation, while the *syphilitic* readily yield to salvarsan (arsphenamin) and iodids. Exposure to sunlight and ultraviolet rays is advocated for the *tubercular affections* of the colon.

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CONSTIPATION

Definition.—Constipation (costiveness) is a disturbance of intestinal function, usually of the colon, which results in delayed or incomplete evacuation of the feces.

Incidence.—Constipation is a frequent disorder, often causes ill health, and because of the unhygienic conditions of modern living, is increasing. Lack of fresh air and exercise, over-refined foods, and nervous tension are important contributing factors. Obstipation due to angulation, *redundant* colon, pressure from tumors or adjacent organs, or to more or less complete obstruction of the intestine is not infrequent, but a great majority of cases are the result of disordered function. The normal progress of the intestinal contents is accomplished by a succession of peristaltic waves running from above downward; stimuli of mechanical or chemical origin from within the gut cause contraction above and relaxation below the point of stimulation. This is influenced by the tone of the muscles and the vegetative nervous system, which is, in turn, influenced by the endocrine glands. Disturbances in the excitability and fatigue reactions of the non-striated muscles of the intestines are, therefore, frequent.

Etiology.—Constipation is most often produced by a diet which leaves insufficient undigested residue, sedentary habits, irregular hours for defecation, and inattention to the "calls of nature." When constipation develops it is usually aggravated by the use of cathartic drugs, which, in turn, cause or increase inflammation of the large intestine (colitis). Essential constipation, which is usually a family complaint, is due not to organic defects, but to a derangement of the peristaltic mechanism. It is not very common.

The causes of constipation have been grouped by Kast into the following classes: mechanical, dyschesetic, inhibitory, and functional. The *mechanical causes* include pressure on the intestines by abdominal or pelvic tumors; invagination, volvulus, and kinks; stenosis from ulcers and scars (tuberculosis, syphilis) or tumors (carcinoma, sarcoma); and passive congestion due to circulatory failure. *Dyschesia* is difficulty in expulsion of feces from the rectum and results from impairment of the rectal reflexes, inhibitions of local origin (fissure, fistula, hemorrhoids, prostate), or weakness of the pelvic floor (laceration). The *inhibitions* which arise in the nervous system or in the intestinal tract may be associated with mental or spinal disease, endocrine dysfunction, hysteria, neurasthenia, cholecystitis, appendicitis, colitis, peritonitis, and perimetritis. The *functional* causes of constipation include such toxic conditions and disturbances of nutrition as fever, lead poisoning, anemia, cachexia, malnutrition, and fatigue; impairment of muscular tone which may be in the nature of either a decrease (hypotonic or atonic constipation) or an increase (hypertonic or spastic constipation); deficient stimulation of the intestines when the food residue is too small, the secretion of bile diminished, or the gastro-intestinal secretions disturbed.

Symptoms.—Constipation may for a long time impair the health very little; sooner or later, however, it causes anorexia, coating of the tongue, lassitude, and mental depression. Headache, vertigo, anemia, acne, and other affections of the skin are frequent symptoms. Neuritis, neuralgia, and arthritic pains often follow. There is usually indigestion, particularly a sense of fulness after meals, eructation of gas, and distention of the abdomen. When persistent, the accumulation of feces leads to colitis, ulceration of the colon or rectum, and the formation of diverticula, hemorrhoids, and fissures. Resulting infection of the wall of the gut may incite the formation of connective tissue and adhesions to contiguous structures. From such foci, infection may be carried through the lymphatics or the blood to secondary localizations in the urinary tract, gall-bladder, joints, and other tissues. Sometimes the fecal mass becomes channelled and diarrhea may occur. Fever is an occasional symptom.

Constipation is often classified as atonic or spastic (hypertonic), a division which is useful in diagnosis and treatment. The *atonic type* occurs in individuals of sedentary habits who eat too much and have become obese and flabby. Examination of the abdomen reveals lax muscles and moderate distention with gas. The colon cannot be palpated. Constipation with *spasticity of the colon* occurs in nervous people with active reflexes who are frequently under weight. The descending and sigmoid portions of the colon can be felt as a firm cord which is often tender to pressure. In severe cases part of the transverse colon can also be palpated, and the cecum splashes on clapotage because of retention of fluid with gas; this usually indicates dilation of the cecum from back pressure.

Diagnosis.—The diagnosis of constipation depends on the demonstration of abnormal delay in evacuation of the feces. The simplest method is to give 10 grains of carmine in a capsule. The stools normally become colored in twenty-four to forty-eight hours and the pigment should be eliminated within forty-eight to seventy-two hours. The presence of carmine in the feces more than seventy-two hours after ingestion indicates abnormal intestinal retention. It is most important to determine the cause of stasis

in every case. Examination of the rectum is essential. Severe cases with constitutional symptoms demand *x*-ray and sigmoidoscopic examinations as well. The only symptom of carcinoma of the rectum or sigmoid flexure may be constipation.

Prognosis.—Constipation, if treated early, is a curable disease except for the essential type. When due to organic conditions, such as strictures, kinks, and bands, surgery usually gives complete relief. If extensive changes have developed in the wall of the gut the outlook is less favorable; when complicated by ulcerative colitis, cure is seldom possible, although the condition may be much improved. Accurate diagnosis of the cause and nature of the constipation is of great importance, and so also is early treatment. This is especially true when constipation begins in childhood, for it may become serious and at that period can usually be relieved.

Treatment.—The treatment varies with the cause and type of constipation. When it is the result of organic obstruction (bands, tumors in the wall of the gut or outside), or diseased conditions of the pylorus, gall-bladder, appendix, rectum, and anus, appropriate surgical treatment is necessary. In all cases which are clearly functional in origin or are the result of slight mechanical interferences, regular adequate evacuation should be re-established by regulation of the diet, insistence on hygienic measures and exercises, and cessation of the use of drugs. Much may be accomplished by systematic habits, particularly in the young. The patient should go to stool at a fixed hour every day, whether there is desire or not, and the desire should always be granted. Water should be taken freely, one or two glasses on arising and before retiring; one glass of cool water with each meal aids digestion and at least one glass should be taken between meals. Exercise in moderation, preferably out-of-doors, is desirable. Patients with lax, weak, or thin abdominal muscles are benefited by appropriate strengthening exercises. Massage of the abdomen is invaluable, especially for atonic constipation. A good substitute is a metal ball weighing from 4 to 6 pounds, which may be rolled over the abdomen every morning for five or ten minutes. None or all of these measures, however, will restore the function to normal unless the diet contains a large quantity of undigestible material. Whole wheat bread, Graham bread, bran muffins, or cooked bran; cooked and raw vegetables such as lettuce, celery, endive, spinach, string beans, carrots, and beets; cooked fruits, especially prunes, apricots, cherries, and plums; figs, dates, raisins, and nuts should all be included. Raw fruits and fruit juices should be given sparingly, except in early and mild cases. Marmalade, honey, jams, and milk sugar often help by increasing fermentation. Lactic acid bacilli, *Bacillus acidophilus*, and yeast are widely used, with occasional benefit; they are most apt to help when the intestinal flora includes many anaërobes. Changes in diet and stimulation of the motor activity of the intestines accomplish the desired transformation to an aciduric, Gram-negative type of flora more quickly and satisfactorily than does the ingestion of bacteria. Cultures are of little value unless they are administered in very large quantities and a proper pabulum is provided for their growth within the intestines. Mineral oil and agar-agar are both exceedingly useful as they increase the bulk without irritating the mucous membrane. A tablespoonful of oil taken once or twice daily when the stomach is empty often relieves the milder cases. One or two dessertspoonfuls of agar-agar with two meals a day is a useful adjuvant. Although in no way harmful, ingestion

of such materials should be regarded as a temporary measure to be continued only until dietetic and hygienic habits can be corrected.

The above directions apply particularly to mild or moderately severe cases of the atonic type. Mild examples of the spastic type may be treated similarly except that the stimulation should not be too hurried or strong at first. Better results are obtained by omitting all uncooked foods at the beginning of treatment and gradually adding, first vegetable salads, and later raw fruits. Antispasmodic measures such as hot, moist compresses, oil enemata, and belladonna (by mouth or in a suppository) are helpful. Small doses of bromids or luminal are advisable for nervous patients. The spastic type is frequently complicated by colitis, and treatment will be futile or harmful unless this is recognized and cured first by a bland diet and sedative measures. Curing the colitis often relieves the constipation without further treatment.

Many people wrongly harbor the idea, which often becomes an obsession, that their bowels do not move with sufficient frequency or completeness. Reassurance on this point is desirable before beginning treatment. It is very helpful to convince them, if possible, that if their bowels do not move at a certain hour, they doubtless will at a later time and, therefore, not to worry about it. They should understand that an effort is being made to re-educate their intestines and it is not to be expected that they will at once resume a normal rhythm. After forty-eight hours have passed without an evacuation, the simplest measure is the rectal injection of 8 to 16 ounces of plain luke-warm water or of normal saline solution. Other ingredients such as soap, glycerin, ox-gall, and turpentine should be avoided, as they act by producing local irritation and may cause or continue inflammation of the rectal and anal mucous membrane. High enemas and colon irrigations, when properly given, are also useful, particularly when constipation is complicated by colitis. The patient should lie on his back (some authors prefer the right lateral position) with the hips elevated 8 to 12 inches. The rectal tube should be introduced only 4 inches and the container should not be raised more than 3 feet above the anus. The fluid should run slowly and be controlled by compression of the tube.

In essential constipation and in some cases of habitual constipation it is necessary to give drugs. Of all the laxatives, cascara is the most satisfactory; it may be used for years without harm. Phenolphthalein acts well in many cases and in small or moderate doses causes little catarrhal inflammation of the intestines. Aloes, senna, and rhubarb should not be given for very long, although they may be useful as an occasional laxative.

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VISCEROPTOSIS

(*Splanchnoptosis, Glenard's Disease*)

Definition.—Splanchnoptosis is prolapse or falling of the viscera. Ptosis or falling of a single organ is comparatively rare, the stomach (gastroptosis), intestines (enteroptosis, coloptosis), and also the kidneys (nephroptosis) and liver (hepatoptosis) usually being involved. Visceroptosis was formerly regarded as a distinct disease, but now it is considered a manifestation of a general constitutional disturbance associated with asthenia or atony of most, if not all, of the smooth muscles of the body.

Etiology and Incidence.—Visceroptosis is of two types: congenital and acquired. The latter type probably develops only in individuals with a congenitally asthenic build or constitution. Although visceroptosis is commonly first recognized in adults, it may exist at birth and is doubtless present in many children. It is much more common in women than in men (10 : 1), and is found in about 20 per cent. of women.

A study of old paintings, notably Botticelli's women, makes it evident that the condition has existed for centuries. The incidence is believed to have increased in recent times. Visceroptosis has been reported to exist in practically all races, including those among whom tight clothing is unknown. Repeated pregnancies, recurring ascites, or large abdominal tumors, followed by relaxation and sagging of the abdominal wall, are causes for the acquired form. Tight garments and constipation may also play a part. Defects in posture certainly predispose to ptosis and if uncorrected may result in pronounced sagging in the congenitally susceptible. Acute and chronic infections (tuberculosis, syphilis), enterocolitis, undernourishment, and a sedentary life, by inducing relaxation and atony, may result in the acquired form. Inheritance doubtless enters into the causation, as well as do endocrine disturbances. The chief etiological factors are, therefore, an inherited or congenital constitutional state, and loss of muscle and nerve tone because of faulty development, stretching of the supporting structures, faulty hygiene, undernourishment, or infection.

Symptoms.—Many individuals with marked visceroptosis experience few or no symptoms. Some have unconsciously adapted themselves to a state of lessened endeavor and efficiency which, by reducing nerve strain, prevents the development of symptoms; others have symptoms only when they exceed their constitutional capacity. The nature of the symptoms depends upon the organs chiefly involved. They are frequently numerous and varied. It is most important to understand that the presence and severity of the symptoms depends chiefly on the *function* of the organ or organs involved and not upon their *position*. Even when the greater curvature of the stomach lies in the pelvis there may be no symptoms if the emptying time is normal; slight ptosis may, on the other hand, evoke severe symptoms when the motility is impaired.

Patients complain of backache, undue fatigue, cold extremities, and palpitation of the heart. They are often neurasthenic and sometimes psychasthenic. The duties of life are accomplished with difficulty and "nervous breakdowns" are not uncommon. The usual subject is a young person of slight build who is thin, pallid, and nervous. The normal lordosis of the lumbar spine is increased, there is compensatory relative kyphosis of the dorsal spine, and the scapulæ are prominent or "winged." The costal

angle is acute, the abdomen is prominent, and the muscle wall is thin and atonic. In pronounced cases there is flattening of the epigastrium and bulging of the hypogastrium. Peristaltic movements of the intestines and pulsation of the aorta may be observed. Floating of the tenth rib is accorded significance by some authors. The symptoms are aggravated by walking or standing and may be relieved by lying down or by supporting the abdominal wall. The local symptoms depend on the viscera involved.

Gastroptosis was formerly thought to be frequent, but more extended use of the *x*-ray has demonstrated that ptosis of the stomach as a whole is uncommon and that its normal position is not what was formerly supposed. The symptoms are anorexia, coating of the tongue, flatulence with a sensation of weight or fulness after meals, sometimes nausea and vomiting, dull pain in the epigastrium, and sometimes acidity. Constipation is the rule; headache, a sense of distention of the eyes, and insomnia are frequent manifestations. It is essential to determine the functional capacity of the stomach by a test-meal, *x*-ray examination, and analysis of the stools. Delay in the emptying time is usual, and the secretions are altered.

Nephroptosis of various degrees is very common (20 per cent. in women and 2 per cent. in men), but in only one case in ten are there distinct local symptoms. Among the symptoms are pain in the flank and back, which may be either continuous or intermittent, and frequent urination with dysuria, which is relieved by lying down. These are generally accompanied by gastric symptoms. Acute attacks of intense pain with vomiting (*Dietl's crises*) occasionally occur. They are usually thought to be due to intermittent hydronephrosis, though some authors believe that they result from torsion of the renal vessels and nerves.

Some degree of *ptosis of the intestines*, particularly of the colon, is found practically whenever any of the abdominal viscera are displaced. Coloptosis retards drainage, and leads to fermentation, putrefaction, and inflammation of the wall, usually, though not always, confined to the mucous coat. The colon, most frequently the sigmoid portion, is often redundant; this contributes to stasis. These conditions can be ascertained only by *x*-ray examination of the gut after it has been filled with opaque material. The symptoms are anorexia, coating of the tongue, flatulence, sensations of fulness and dragging in the abdomen, backache, and constipation, which may be very severe. Attacks of diarrhea may alternate with constipation. Mucous colitis is quite common. Undernourishment and loss of weight with secondary anemia follow and doubtless aggravate the condition. Neurasthenia frequently ensues and complicates the effective treatment of these patients.

Ptosis of the liver (hepatoptosis) *and spleen* (splenoptosis) are occasionally observed. Ptosis of the pancreas has been reported. Dragging sensations, sometimes painful, are the only suggestive symptoms, as the functions of these organs are apparently not disturbed.

Diagnosis.—Visceroptosis should be suspected when a person with the characteristic habitus and the neurasthenic cast of mind complains of a variety of abdominal symptoms. It should be remembered, however, that all patients with *habitus enteropticus* do not have ptoses, for increasing experience with *x*-rays has proved that the condition is not as common as was formerly assumed, and that many people with ptoses have no symptoms. Displacement of the solid organs can be determined by bimanual palpation

with the patient in prone and upright positions. *x*-Ray examination is essential for accurate location of the stomach and intestines.

Prognosis.—It is doubtful if ptosed viscera can be restored to a normal position and held there except by surgery. The prognosis for complete restoration of health is, therefore, doubtful and relapses are very common. The symptoms, however, can generally be relieved if the patient will cooperate faithfully and follow a careful régime indefinitely. As the condition depends on a constitutional state, patients should be protected from infections and exhausting illnesses of all kinds. Children with the characteristic bodily conformations should be carefully observed and trained to develop the highest degree of muscular tone and physical efficiency. Dietetics, rest, exercises, massage, and an out-of-door life should all be prescribed as the need arises.

Treatment.—The main object of treatment is to improve the nutritional state and to restore or improve muscle tone. The most effective therapeutic measure is exercise. It may be necessary to begin with passive exercises and massage, but active exercise designed to strengthen the abdominal, pelvic, and lumbar muscles should be started as soon as possible, and very gradually increased in severity and duration. An intelligent trainer (there are only a few) can accomplish more than medicines, belts, or surgery. The diet must have a high caloric content and supplementary feedings are usually indicated. It is also essential to determine the functional capacity of the digestive organs, particularly the motility, and to adjust the diet accordingly. Constipation and colitis are common symptoms which must be properly treated; when these are relieved most of the other symptoms disappear. Hydrotherapy is often helpful. Rest after meals is desirable; elevation of the foot of the bed is recommended.

Mechanical support of the lower part of the abdomen often gives prompt relief, although *x*-ray studies usually fail to demonstrate that this changes the position of the viscera. Many kinds of belts, corsets, and binders have been devised for the purpose and are all about equally effective. A light girdle which fits tightly about the hips and lower abdomen is generally satisfactory if it is adjusted while the patient is in a recumbent posture.

Alkalies, hydrochloric acid, bitter stomachics, iron, or arsenic may be administered as seems necessary. The best possible hygiene should be maintained and it is most important to search for and eradicate all focal infections.

Surgery is seldom needed. Very rarely it may be advisable to suspend a single organ, but the results do not warrant confidence in the procedure.

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DISEASES OF THE DUODENUM

Ulcer is the commonest affection of the duodenum, but more frequent use of the *x*-ray has demonstrated that other lesions are not at all uncommon. They may provoke distressing symptoms.

Duodenitis is a catarrhal inflammation of the duodenum which is usually associated with catarrhal gastritis or cholecystitis. When the process extends into the common bile-duct jaundice may result. The diagnosis cannot be made independently of other affections.

Stricture of the duodenum may result from inflammatory adhesions, cicatricial contraction, congenital abnormal folds of the anterior mesogastrium, pressure from the mesenteric vessels, and tumors in the wall or in adjacent organs. Congenital stenosis of the duodenum has been reported. Stricture causes dilation proximal to the lesion, and stasis of the contents with disturbances of digestion. Dilation of the stomach, acute or chronic, may ensue.

Symptoms.—The symptoms are a sensation of heaviness or pressure in the epigastrium which comes on two or three hours after meals, especially if they are large and include coarse foods. Nausea is frequent, although vomiting seldom occurs unless the obstruction is considerable. The epigastrium becomes distended and often tender; frequent belching may become distressing. There may be attacks of pain in the epigastrium or right hypochondrium which, in radiation and severity, suggest biliary colic. Slight or moderate jaundice may follow such attacks. In the congenital cases there is usually a history of digestive disturbance, with impaired nutrition, dating from childhood. Although the symptoms are intermittent in early life, they eventually become almost continuous. Loss of weight and anemia ultimately develop.

Carcinoma of the duodenum is practically always primary. While it is relatively uncommon, it constitutes about 50 per cent. of cancers of the small intestine. It is rather more frequent in males than in females. The symptoms, which differ with the location of the tumor, depend primarily on its relation to the papilla of Vater.

Suprapapillary growths produce in general the symptoms of pyloric obstruction: dilation of the stomach and vomiting of stagnant contents, and sometimes of blood. Free hydrochloric acid is present and lactic acid is not produced. In half of the cases a mass may be palpated. When the tumor is located near the papilla (*circumpapillary carcinoma*) and involves it, there are, in addition, the symptoms of obstructive jaundice. *Infrapapillary carcinoma* is characterized by symptoms of obstruction with vomiting of bile and pancreatic juice.

Diverticula occasionally develop in the duodenum. While they are commonly thought to result from ulcers, no such cause can be demonstrated in numerous instances. They are usually small, but sometimes assume considerable size and cause pronounced stasis of the duodenal contents. Rupture is rare.

Perforation of the duodenum may result from an ulcer, a diverticulum, trauma, or operation. The symptoms are those of shock followed by peritonitis.

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DIVERTICULA OF THE INTESTINES

(*Diverticulosis*)

Meckel's Diverticulum.—The omphalomesenteric duct normally disappears within a few weeks after birth, but it occasionally persists more or less completely as a fibrous cord or tube with the same morphology as the ileum. It arises from the vicinity of the ileocecal junction and may be attached to the umbilicus, or it may have no distal attachment and move freely in the abdominal cavity. It may produce no symptoms, but at times it causes volvulus, strangulation, or intussusception. Neoplastic degeneration is not uncommon.

Diverticula may be congenital, but most of them are doubtless acquired. They may develop as small pouch-like protrusions of any part of the intestines, especially in the descending and sigmoid portions of the colon. Formerly considered rare, they are now known to occur frequently. This has been demonstrated by *x*-ray examinations. They may occur singly, but are usually multiple, and are often very numerous, particularly in the colon, where they usually develop in two parallel rows on either side of the mesocolon. Diverticula of the small intestine occur most often in the duodenum and ileum.

Etiology.—Diverticulosis most often develops in middle life. Increased intracolonic pressure induced by constipation and cathartics, especially in obese, sthenic individuals, is believed to be the cause and to favor the enlargement of diverticula. Feces collect in the sacs and become subject to bacterial action which inflames the walls. They may thus become serious foci of infection and intoxication.

Symptoms.—Diverticula may cause no symptoms, or they may aggravate constipation and intestinal intoxication. Not infrequently, however, they become acutely or chronically inflamed. The symptoms of *acute diverticulitis* are similar to those of appendicitis, except that the local manifestations are usually in the left lower abdominal quadrant. Pain, tenderness, rigidity of the abdominal muscles, fever, and leukocytosis constitute the syndrome. Vomiting sometimes occurs; constipation is usual, although diarrhea may develop. Except when concealed by meteorism a tumor can usually be felt in the left lower quadrant of the abdomen. Occasionally an abscess forms which may discharge through the bowel or, rarely, through the abdominal wall.

A *chronic inflammatory process* originating in a diverticulum may result in great thickening of the wall and cause partial obstruction of the colon. This is frequently mistaken for carcinoma.

Diagnosis.—Diverticula are frequently discovered in routine *x*-ray examinations of the gastro-intestinal tract. This is the only method by which they may be definitely diagnosed. The barium or bismuth used for this purpose remains in the sacs for a long time, even weeks or months.

Prognosis.—In the great majority of cases diverticula produce few or no symptoms and are accidentally found. Perforation occurs very rarely. Inflammation (diverticulitis and peridiverticulitis) is not uncommon, but it usually subsides with treatment. An abscess occasionally develops, and rarely chronic inflammation with connective-tissue formation produces sufficient obstruction to require operative treatment.

Treatment.—The treatment is usually medical. To limit the formation

of diverticula and prevent complications it is necessary to stop purgatives and secure evacuation of the bowel by mechanical means. Administration of mineral oil and agar in liberal doses with a diet containing a large indigestible residue is usually sufficient. An enema may occasionally be necessary. Because it seems preferable to have the sacs filled with a bland non-toxic substance rather than with feces undergoing putrefaction, bismuth or barium is administered by mouth at stated intervals. One ounce of bismuth subcarbonate or barium sulphate once a week lessens whatever local and general symptoms may exist.

For diverticulitis the patient should be kept in bed with hot fomentations over the abdomen. When the tenderness is localized an ice-bag is preferable. The diet must be bland and enemas should be employed for emptying the colon. The formation of an abscess demands incision and drainage. Resection of a portion of the colon is rarely necessary for relief of an obstruction.

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DILATATION OF THE COLON

There are four types of dilatation of the colon. The *first* is entirely gaseous. This generally results from toxic paresis of the gut, although it sometimes appears to be due to mechanical causes, such as handling of the colon in abdominal operations. Marked dilatation is usually associated with general peritonitis, and in some degree with inflammatory processes in the pelvis. In the course of pneumonia, typhoid fever, or sepsis it becomes a serious complication, both because it indicates a severe intoxication and because it interferes with respiration and the circulation. It may also develop in heart failure with congestion in the splanchnic area. The *second type* of dilatation includes distention of the colon by obstruction distal to the dilated gut. Neoplasms, volvulus, and foreign bodies (rarely gall-stones) may cause the colon to reach a very large size. Thrombosis of the mesenteric vessels or a twist in the mesocolon occasionally causes acute dilatation. The *third type* is that in which atony of a portion (most commonly the sigmoid and rectum) or of the entire colon results in very marked dilatation with stasis of the contents. This condition is most often found in females, often in quite young individuals, with weak and relaxed abdominal walls and curvature of the spine. It is probably congenital or at least the result of congenital predisposition. The *fourth type* is *Hirschsprung's disease* or *megacolon*. This condition is usually termed "congenital idiopathic dilatation of the colon," but the studies of Hurst and W. J. Mayo cast doubt upon the accuracy of this conception. Both of these authors believe that the origin of the trouble lies in the pelvi-rectal region and that the dilatation is secondary to a partial obstruction at that point caused by failure of co-ordination

in the non-striated muscle-fibers. Mayo concludes that the condition is analogous to cardiospasm and pylorospasm. Hurst suggests that when the colon becomes dilated it overhangs the undilated portion below and causes stasis of the feces, which results in hypertrophy of the muscle-fibers and final loss of all peristalsis.

Symptoms.—The characteristic symptoms of Hirschsprung's disease are obstinate constipation dating from birth or early infancy and progressive distention of the abdomen. Abdominal distress is common, but acute pain is rare. There are sometimes attacks of colic followed by diarrhea. Gastric disturbances develop and malnutrition follows. The patient dies of inanition, obstruction due to volvulus, or occasionally of perforation of the bowel. Patients usually die early, but a few attain adult life. The entire colon is usually enormously dilated, although occasionally the sigmoid is alone involved. The diameter of the bowel may be 10 or 12 inches.

Treatment.—Obstruction at the pelvi-rectal region demands operation as soon as possible. In most cases surgical intervention is delayed too long. Resection of the dilated portion or of the entire colon is the usual procedure, often preceded by ileostomy. The occasional patients who reach maturity with reasonably good health should be spared surgery.

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INTESTINAL SAND

Intestinal lithiasis is most commonly associated with mucous colitis and diverticulosis. It consists of reddish, gray, or black sand-like particles which may be discharged in small or large quantities. The material contains various organic and inorganic substances, including considerable urobilin, but little pigment. It is, therefore, probably formed in the large intestine and is associated with catarrhal inflammation of that organ.

False intestinal sand resembles true sand, but differs from it in that it is composed of various residues of vegetable foods.

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COLITIS

Definition.—Inflammation of the large intestine may be either acute or chronic. The inflammatory process is usually confined to the mucosa, but may spread to the other layers of the colon. If the peritoneal coat becomes involved, adhesions to contiguous peritoneal surfaces result. The essential cause is bacterial or parasitic infection. Stasis is doubtless a predisposing factor of importance, especially in the chronic forms.

Etiology.—Inflammation of the colon frequently accompanies diarrheal diseases and generally occurs with organic diseases of the colon. It is sometimes a secondary manifestation of certain infectious diseases, such as septicemia, pneumonia, smallpox, measles, and influenza, and also of nephritis, particularly with uremia. The causes of the acute form are similar to those of diarrhea. Except when it is due to *Bacillus dysenteriæ*, *Bacillus enteritidis*, or *Entamœba hystolytica*, no specific organisms are found.

Chronic colitis seldom develops unless there is stasis of the contents of the colon. Constipation is, therefore, the most important predisposing factor. Chronic colitis is a very common condition in patients with more or less pronounced functional disturbance of the nervous system. It was formerly regarded as a secondary effect, but is now more generally thought to be an important cause of nervous affections. Inflammation of the mucosa doubtless permits absorption of toxic substances which are always present in the colon as the result, chiefly, of bacterial action on the remnants of food. Infection of the wall of the gut results in pathological changes and symptoms similar to those occurring elsewhere in the body, and the process is subject to similar exacerbations and remissions. Some of the symptoms are also due to circulatory changes in the abdominal viscera and to reflex radiation from the colon. Chronic appendicitis, cholecystitis, or infection of the uterine adnexa commonly cause spastic constipation and therefore predispose to colitis.

Morbid Anatomy.—The mucous membrane of the colon shows the usual evidences of catarrhal inflammation. In chronic cases the mucosa and sometimes the deeper layers become thickened, and they occasionally undergo follicular ulceration. Pigmentation, hemorrhagic extravasations, and polypi may develop. Mucus is always formed in excess; in acute colitis it is seen in small sago-like masses, sometimes flecked with blood, while in the chronic condition it forms large tenacious threads or patches, gray or yellow in color. Extensive membranes or even casts of the bowels are occasionally seen, particularly in *mucous colitis*.

Symptoms.—Acute.—The onset of acute colitis is usually rather abrupt, with diarrhea, colic, and general tenderness of the abdomen. The stools contain an abundance of mucus and are often tinged with blood. Considerable hemorrhage sometimes occurs. There is little or no fever, but the patient becomes rapidly prostrated and may pass into a state of collapse. Vomiting is not infrequent at the onset, but seldom continues. Thirst, anorexia, and rapid loss of weight follow. When the rectum and anus are involved, the stools become very frequent, and tenesmus accompanies defecation.

Acute colitis lasts from two to five days or more, depending on the previous condition of the patient and the treatment. It may lapse into the chronic form. Recovery is the rule, but elderly patients and those debilitated by chronic diseases or severe acute infections may die from exhaustion.

Chronic colitis is a common affection. Constipation of the spastic type is a usual symptom, but this may alternate with short periods of diarrhea with abdominal pain. The contracted colon may be palpated, most often in the sigmoid portion, and there is tenderness in the part which is especially involved. The appetite is poor and eructations of gas are frequent. A moderate degree of abdominal distention is often found. The patient is

apt to be poorly nourished and complains of various functional disturbances of the nervous system; these often dominate the clinical picture and obscure the intestinal condition. Disturbances of the endocrine glands often accompany and sometimes precede the colitis. When it is recalled that in colitis the wall of the large intestine is usually infected with pathogenic bacteria, the frequent complication by arthritis, neuritis, neuralgia, migraine, anemia, and pyelitis is readily understood. The diagnosis is established by tenderness of the contracted colon and by fecal examinations which reveal the presence of excess mucus. The bacterial flora is changed, a fact which can be established only by careful and laborious bacteriological studies. Proctoscopy and sigmoidoscopy reveal the nature of the process in accessible portions of the tract. The disease is essentially chronic and cure is difficult; relapses are not unusual.

Mucous colitis (*membranous colitis, mucous diarrhea, mucous colic*) was formerly regarded as a neurosis, but clinical and pathological observations now justify the conclusion that it is a form of chronic colitis. It frequently, though not invariably, occurs in patients with enteroptosis. Spastic constipation is always an accompaniment. It is far more common among women than among men, and the sufferers are often highly neurotic. All the causes of spastic constipation predispose to mucous colitis.

The condition is characterized by paroxysms of very severe colic with general abdominal distress, followed after some hours by the passage of large quantities of mucus either as a coating to hardened fecal matter or more often alone. This mucus is usually in the shape of strings or bands and occasionally forms sheaths or casts of the colon. It is frequently tinged with blood; free hemorrhage sometimes occurs. The passage of mucus may be followed by diarrhea for a few days. During the paroxysms the abdomen is distended and very tender, and there is often slight fever with moderate leukocytosis. This arouses the suspicion of acute, localized inflammation. Between attacks the patient complains of indigestion, flatulence, and constipation. Nervous manifestations are usually well marked and the nutrition is impaired, sometimes seriously. Like other forms of chronic colitis, the condition, although it seldom endangers life, is difficult to cure and causes serious states of semi-invalidism.

Treatment.—Rest, a light diet, hot moist applications to the abdomen, and administration of remedies which allay irritation and check peristalsis are the important means of controlling *acute colitis*. Unless the evacuations have been very numerous, large, and watery, it is advisable first to give castor oil (1 oz.). Other appropriate therapeutic measures have been considered in the section on Diarrheal Diseases.

For *chronic colitis* the general hygiene and diet are the most important considerations. The environment and habits of the patients demand careful consideration and correction in so far as is possible. Most patients are better away from home and should be treated in a nursing home or sanitarium during the early stages. Since rest is so important, they should be kept mostly in bed for the first two or three weeks. Hot moist applications (Priessnitz dressings) should be applied to the abdomen for thirty minutes after each feeding. Small doses of mild sedatives allay the irritability of the colon as well as quiet the nervous system as a whole. Luminal (gr. $\frac{1}{4}$ to $\frac{1}{2}$) or bromids (sodium or strontium bromid, gr. v) should be given alone or combined with the tincture of belladonna

(ɱv–x) every three or four hours. Plenty of fresh air is always important. After the more marked symptoms have subsided, exercise should begin. The patient must be gradually brought back to activity out-of-doors. Plenty of rest and exercise, and regularity in all things—eating, defecating, working, and playing—are necessary to prevent relapses. Hydrotherapy, massage, and other forms of physical therapy are useful adjuncts.

The condition of the gastric and intestinal digestion must be considered and suitable treatment devised. Colitis secondary to achlorhydria is readily relieved by the administration of dilute hydrochloric acid (ɱxx–lx well diluted, with and after meals). Pepsin, pancreatic extracts, and bile salts are sometimes useful but feeble aids. The most important and fundamental factor in the treatment of chronic colitis is the diet. An inflamed, swollen, possibly ulcerated mucous membrane must be freed from irritation in so far as possible. The difficulty of fully accomplishing this renders cure difficult. When all defects of digestion in the stomach and small intestine have been corrected as far as possible, the next step is to regulate the diet so that a minimum of irritating substances reaches the large intestine. A good example of such a diet is the following, which is recommended by Alvarez:

Breakfast

Orange juice; grape fruit (avoid the fiber).
Cantaloupe and melons are inadvisable, as they tend to regurgitate for hours.
Coffee in moderation; chocolate; cocoa or tea.
One or two eggs with ham or bacon (avoid the purely fibrous part).
White bread and butter; toast or zwieback.
Any smooth mush, such as farina; germea; cream of wheat; cornmeal or strained rolled oats.
Puffed cereals and corn flakes are also allowed.
Shredded wheat biscuits and other coarse breakfast foods are not allowed.

Lunch or Dinner

Broths; bouillon; cream soups; chowder.
Small portion of meat, fish, oysters, chicken, or squab (avoid the fibrous parts and gristle).
No smoked or canned fish, or pork.
Avoid veal, crab, and lobster if they seem to cause indigestion.
White bread and butter; hot biscuits made small so as to consist mainly of crust. No rough bran breads or bran biscuits.
Rice; potatoes—baked, mashed, hashed-brown, or French-fried; sweet potatoes; hominy; tomatoes stewed, strained, and with cracker crumbs; well cooked cauliflower tops with cream sauce; and asparagus tips. Later may try brussels sprouts. Italian pastes; noodles; macaroni or spaghetti, cooked soft with a little cheese or cream sauce.
Purées of peas; beans; lentils; lima beans or artichoke hearts. All skins or fiber should be removed by passing through a ricer. "Kornlet" in cans furnishes sweet corn without the indigestible husks. There are practically no other vegetables that can be puréed to advantage. Spinach often causes trouble and is not recommended. Bananas can be fried in butter or baked in their skins. String beans are allowed if young and tender. No salads at first. Later you may try a little tender lettuce with apples or bananas, tomato jelly, or boiled egg. Mayonnaise and French dressing are allowed.

For Dessert

Simple puddings, custards, ice-cream, jello, plain cake, canned or stewed fruit. Avoid cheese, nuts, and raisins.

If constipated, stewed fruit may be taken once or twice a day. In winter the dried pared fruit may be used for stewing. Too much sugar should not be added. Apple-sauce is much more palatable if made from unpared and uncored apples. The sauce is strained later. It may be diluted with a little tapioca or sago. The apples may be baked. Blackberries and loganberries can be stewed and strained, and the sweetened juice

thickened with cornstarch. This makes a delicious dish with the full flavor of the berries. Canned fruits, such as pears and peaches, are allowed. Later the patient may try a fully ripe pear, peach, or apple.

Avoid most of the green vegetables, salads, and raw fruits.

Avoid sugar in concentrated form; take no candy or other food between meals.

As the inflammatory process subsides foods which contain a large residue of undigested material are gradually added to the diet until eventually most of the food contains a large residue, such as that recommended for atonic constipation. In order to prevent recurrences and maintain the general health, it is essential that the bowels should move adequately without the use of purgatives in any form. As the disease is generally the result of pernicious purgation, continuation or resumption of the habit will invariably result in a relapse.

It is important that stasis and fecal accumulation should be prevented, particularly during the earlier period of treatment. This is best accomplished by daily administration of an enema of not more than 1 pint of warm sterile water or normal salt solution. The rectal tube should be inserted only 3 or 4 inches and the injection given while the patient is seated on the toilet. So-called high enemas or colon irrigations are useful, particularly at the beginning of treatment, when the colon is not highly irritable or spastic. It removes the contents of the gut and cleanses the mucous membrane. The irrigation should be preceded by a low enema to clear the rectum and sigmoid colon. During a colon irrigation the patient should lie on his back with the knees bent and the hips elevated about a foot by a pillow. The rectal tube should be inserted only 4 inches and the water bag must not be elevated more than 3 feet above the pelvis. The fluid should be allowed to flow in very slowly, the rate being controlled by compression of the tube, in order to avoid distention of the rectum. More than very slight discomfort should be avoided, and the irrigation stopped if necessary. In this manner several pints of fluid will gently flow up as far as the cecum. The fluid is allowed to run out through a connecting T-tube, or it may be expelled by the patient. This procedure may be repeated several times at one sitting. It is futile to attempt to pass a tube beyond the rectum, as *x*-rays show that it invariably coils up in the rectal ampulla. Plain water, normal saline solution, or bicarbonate of soda (1 dram to the quart) warmed to body temperature are most used. Mild astringent or stimulating drugs (chamomile tea, mucilage, chlorazene, silver nitrate, ichthyol) may be useful.

For the highly spastic conditions enemata of oil are best. Four to 8 ounces of warm olive oil, cotton-seed oil, or mineral oil are injected and retained for a few hours or overnight. They should be given daily at first, later every other day, and subsequently at longer intervals.

If after the colitis has been cured, the patient is still constipated, the treatment outlined for that condition should be given. Treatment of the colitis, however, frequently entirely relieves the constipation. Systematic rest, gradually increasing exercise, restoration of the tone of the intestinal and abdominal muscles, fresh air, occupation, congenial environment, relief from nagging worries, and the cultivation of equanimity and optimism all play important parts in restoring the chronic sufferer to normal. Good hygiene, rational living, and a reasonable diet are necessary to prevent recurrences.

Medicinal Treatment.—Liquid petrolatum given by mouth (1 or 2 tablespoonfuls), on an empty stomach once or twice daily, is useful because it increases the intestinal bulk, and lubricates and protects the mucosa. Agar-agar (2 to 8 teaspoonfuls twice daily) also acts by increasing the bulk. Neither of these substances should be employed when the colon is highly spastic or seriously involved. In the later stages they are, however, of the greatest aid. Cascara, phenolphthalein, and other laxatives are often combined with agar-agar and for a time act very satisfactorily. It is better to avoid them, however, for they all tend to irritate the intestine.

Castor oil is the ideal cleanser and may occasionally be given with benefit, especially in acute and highly toxic conditions. All saline cathartics, senna, rhubarb, aloes, etc., should generally be avoided in colitis. If, for convenience, it becomes necessary to give some laxative drug, cascara or phenolphthalein is preferable.

Mucous Colitis.—Attacks of so-called mucous colitis are treated by rest and sedative measures. Application of hot moist compresses to the abdomen gives comfort, but in severe cases it is advisable to give a dose of codeine (gr. i–ij) or morphin (gr. $\frac{1}{4}$) by hypodermic. Luminal, bromids, and belladonna are feeble but at times useful aids. After the attack has subsided, the treatment is that of an acute exacerbation of chronic colitis with spastic constipation.

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ACUTE APPENDICITIS

Definition.—Acute appendicitis is an acute inflammatory process involving the vermiform appendix. This may subside spontaneously, though frequently it causes changes in the appendix which predispose to subsequent attacks; or it may result in perforation or gangrene followed by localized or general peritonitis if the appendix is not removed before such changes have occurred. Clinically, acute appendicitis is characterized by cramp-like abdominal pains; localized tenderness and muscular rigidity over the site of the appendix; varying degrees of fever; leukocytosis; and vomiting.

History.—The significance of the lesion was first definitely recognized by Reginald Fitz, of Boston, in 1886. He introduced into medical literature the term "appendicitis," which, etymologically, is badly chosen, for it is made up of a Latin prefix and a Greek suffix. Following his early reports the disease was studied intensively, attention being directed to the clinical course, pathology, and indications for treatment. Long before Fitz published his observations, isolated reports of inflammatory lesions of the appendix, associated with perforation and peritonitis, had been made. Mestivier in 1759 was probably the first to describe and direct attention to an acute inflammatory lesion of the appendix. Parkinson in 1812 found at autopsy a perforation of the appendix of a child that had died after being sick two days. He regarded the perforation as the cause of the fatal peritonitis. Louyer-Villermay in 1824 described in detail the morbid anatomy in 2 cases: in one, in which there was localized inflammation, the appendix was larger and thicker than normal; black and gangrenous; and contained pus; the cecum was not affected: in the other, the appendix was enlarged and dark in color, the distal portion being gan-

grenous. Louyer-Villermay emphasized the fact that inflammatory processes involving the appendix develop and progress rapidly. In 1827 Melier described 5 cases of appendicitis. He laid special stress on the pathogenesis and suggested the possibility of fecal masses as a causative factor. He also states that if the disease was regarded as rare it was because the autopsies were incomplete and sufficient attention was not directed to the appendix. He describes what is probably the first case of appendicitis diagnosed during life and recognized the possibility of a transformation of the acute into the chronic type. These early reports were either overlooked or neglected for a number of years. Dupuytren believed that the inflammatory process developed about the cecum and that it was secondary to mechanical factors, being most frequently observed where the free joins the more fixed portion of the bowel and where the fecal matter becomes thickened. His authority was so great that for years attention was directed to the cecum and adjacent structures in the study of the disease. He introduced the term "*perityphlitis*" to describe the inflammation about the cecum. Some years later more complete autopsies and accurate observations demonstrated the rôle played by the appendix in localized and general peritonitis.

Incidence.—Vital statistics seem to show that appendicitis is on the increase, but this is probably not true. The diagnosis is made more frequently and with greater certainty than before and, as the number of cases reported in vital statistics increases, the number of lesions of the liver and peritoneum decrease. Appendicitis is more common among highly civilized than among primitive people, among dwellers in cities than among those living in country districts. It seems to increase with the restraints and restrictions of civilized life which affect defecation and the passage of gas. Constipation undoubtedly contributes to the development of the disease. Primitive people rarely have appendicitis so long as they live in their original surroundings, but the incidence increases as soon as there is a change in the mode of living; for example, when country people move into the city. It is generally admitted that the disease is rare in the Orient. It is interesting that appendicitis is only one-half as common among the French troops stationed in Algiers and Tunis as among those in France. The incidence among the French born in Algiers and Tunis is one-fifth of that in France. It is stated upon good authority that although appendicitis is not uncommon among Arabs dwelling in cities, it does not attack those who remain nomadic. Naab found it to be much less common among the Asiatic than among the European Turks. This may be due to differences in diet, for the one eats meat only occasionally, and then but little; while the other lives chiefly upon meat. Among the natives of Australia and Sumatra the disease is practically unknown. Statistics do not indicate that the well-to-do suffer from appendicitis any more frequently than do the lower classes. The fecal mass resulting from the digestion of meat is smaller than that following digestion of vegetables and undoubtedly stimulates peristalsis less. The intestinal atony and constipation caused by a small fecal mass are undoubtedly factors which contribute to the causation of the lesion. *Appendicitis* is most often seen in patients between ten and thirty years of age, but it may occur at almost any age. Fenger described a case in a seven-week-old baby, and the writer has drained an appendiceal abscess in a patient over ninety years old. All statistics agree that the disease is more common in men than in women: of 1577 cases, 949 (60 per cent.) occurred in men and 628 (40 per cent.) in women. Appendicitis has been observed in several members of the same family and it has been suggested that there might be a family predisposition to the disease. This is, however, probably not the case; and it is more likely that exposure to the same conditions of life and a similarity in diet account for the occurrence of the disease in the various members of a given family.

Etiology.—The appendix is mechanically predisposed to inflammation. It is lined by mucous membrane, the secretion of which, containing bacteria, is discharged through a narrow lumen into the cecum. Interference with this discharge causes distention of the appendix, which interferes with its vascular supply and favors infection. Experimentally, it has not been possible to produce appendicitis as it occurs in man. Many of the conclusions as to the cause are based upon the study of pathological changes observed in the appendix at different stages of the disease. In discussing the cause, the primary and recurring attacks of the disease should be considered separately. Undoubtedly in many instances the primary attack is so mild as to be unnoticed or soon forgotten, and consequently it is often impossible to determine whether a recognized attack is primary or a recurrence. The majority of cases of primary appendicitis are probably of enterogenous origin, and result from the extension of an inflammatory lesion of the cecum into the appendix. Riedel believes that acute appendicitis develops upon a slowly progressing and insidious disease of the mucous membrane, "*appendicitis granulosa*," which is characterized by the development of granulation tissue between the gland tubules. Small but macroscopically visible hemorrhages, the significance of which will be discussed later, are found in this tissue. They occur most frequently about the follicles or the base of the gland tubules, raise the epithelium, and interfere with the blood-supply of the appendix. Bacteria may invade the lymphatics during such chronic inflammation and set up an additional acute inflammatory process. In the milder types the infection may be non-suppurative, while in the severer forms suppuration or gangrene may occur. Aschoff believes that the inflammatory process begins in the depressions and pits of the mucous membrane where mechanical conditions favor the growth and action of bacteria. At the beginning of the attack there is a small break in the mucous membrane covered by a small mass or plug of fibrin and leukocytes. The inflamed area leading from this primary lesion is usually wedge shaped, the apex of the wedge being directed toward the lumen. In most cases numerous bacteria are demonstrable in the plug at the beginning of inflammation. An intramural abscess may develop, which may rupture into the lumen and produce an ulcer, or externally, and cause perforation of the appendix and peritonitis. It has been suggested from time to time that appendicitis is frequently due to the lodgment of bacterial emboli. The hemorrhages often observed in the follicles are regarded by some as indicative of such a process, but many are undoubtedly of traumatic origin, and take place when the appendix is injured during removal. If appendicitis is embolic and secondary to bacteriemia, it is difficult to determine why the symptoms of infection should subside so rapidly after appendectomy. During epidemics of some diseases, such as influenza, the incidence of appendicitis is known to increase, and it is quite probable that infection has taken place through the intestine. The theory that appendicitis is a disease *sui generis*, comparable to diphtheria or scarlet fever, has not been confirmed by either clinical or pathological studies.

Enteroliths undoubtedly play a considerable rôle in the etiology of appendicitis, principally in the secondary and recurrent types. Fecal matter may be found in the appendix, but only in minimal amounts, for the contents of the normal appendix are rapidly discharged into the cecum, and it is questionable whether fecal matter is normally present. Not infre-

quently the appendix contains brownish material composed of mucus, round cells, epithelium, and a large number of bacteria. If larger than the lumen of the appendix the center of an enterolith is composed of fecal matter; the exterior, for the most part, of mucus. There is not much unanimity of opinion regarding the importance of enteroliths in the causation of appendicitis. An enterolith may either act as a mechanical block, which, by preventing discharge of the secretion of the appendix, causes distention and favors infection, or it may cause perforation by direct pressure. Von Brunn and Aschoff do not regard enteroliths as of very great etiological significance. Aschoff even believes that an enterolith may protect the mucous membrane, for he has observed cases of acute appendicitis in which the membrane, proximal and distal to the enterolith, was gangrenous, while that in contact with the stone was flattened and showed no evidence of inflammation. Some significance should, however, be attached to the causative rôle of enteroliths, for statistics show that they are present in the appendix in a relatively large proportion of the cases of acute appendicitis and that in about 85 per cent. of such cases a destructive lesion develops.

Stenosis.—Alterations in the appendix and stenosis of the lumen, which result from the formation of scars or adhesions, play an important rôle in the etiology of the secondary and recurrent attacks. In many cases the disturbance is at the onset purely mechanical, the contents of the appendix being retained under pressure in the organ or imperfectly discharged into the cecum.

Bacteriology.—The results of bacteriological examination of the contents of inflamed appendices vary, and conclusions should only be drawn from data obtained from the examination of the contents of recently removed appendices. Whether the colon bacillus alone can produce the severe forms of appendicitis or whether it must be associated with other forms of pathogenic organisms is an important question which is still unanswered. In earlier studies the colon bacilli were given prominence, while in recent discussions the pyogenic organisms have received more attention. Of the 138 cases examined by Lanz and Tavel the colon bacillus was present in 105; the streptococcus in 49; a diplostreptococcus in 62; the bacillus of malignant edema in 49; and the pseudotetanus bacillus in 59. Haim regards the streptococcus as the organism that plays the principal rôle in appendicitis; he recovered it in pure culture in 16 cases, the colon bacillus in only 7. Oberndorfer also states that undoubtedly streptococci play an important rôle in the etiology of appendicitis. The fact that colon bacilli may rapidly overgrow other organisms accounts for the significance assigned to their presence. The pus which forms during acute appendicitis caused by the streptococcus is thin, serous, scanty, and odorless, while in mixed infections (colon bacilli and streptococci) it is thick and foul smelling. Colon bacilli occur more frequently in the appendices of older patients, while streptococci are found most often in children and young adults. The mixed infections (colon bacillus and streptococcus) may produce rapid gangrene, while the streptococcus alone may cause the appendix to become markedly adherent to neighboring structures.

Morbid Anatomy.—Appendicitis has been classified in various ways according to its pathology. In some outlines tuberculosis and actinomycosis have been included. An article by Aschoff outlines the more important classifications. It is extremely difficult to correlate the symptoms with

the pathological changes and, clinically, it is impossible to differentiate the various forms which may rapidly pass from one into the other. In some types the inflammatory process involves for the most part the mucous membrane (simple or catarrhal appendicitis), while in others the process is more diffuse (acute diffuse appendicitis) and may affect all the tissues of the appendix.

In *simple* or *catarrhal appendicitis* the grayish-yellow mucous membrane becomes swollen and injected; the secretion is greatly increased in amount; the tissues are infiltrated with round cells and the follicles become more or less swollen. The lumen of the appendix is filled with non-purulent material, and the entire organ is rigid and thickened. There is not always a lesion in the mucous membrane. Healing may take place without any change, but usually results in stenosis after ulceration or kinking due to peritoneal adhesions—residual lesions which predispose to subsequent attacks. This type of appendicitis favors the formation of enteroliths.

In *acute diffuse appendicitis* the inflammation is deeper than in the simple form. The mucous membrane becomes granular. The appendix contains a purulent, mucopurulent, or hemorrhagic secretion. The frequently noted ulceration of the mucous membrane is caused either by the pressure of an enterolith, or by the rupture of an abscess or necrotic follicle into the lumen. The suppurative and gangrenous processes are caused by virulent organisms, and gangrene by thrombosis of the vessels as well. In some instances gangrene develops so rapidly as to suggest embolism.

Symptoms.—The symptoms of appendicitis are here discussed in the order of their importance.

Pain.—The pain develops suddenly and is not infrequently so severe that the patient exhibits symptoms of collapse. It may be epigastric or diffuse, is cramp-like in character and, while it may persist, undergoes definite exacerbations, which are apparently caused by peristalsis. These exacerbations serve to differentiate the pain associated with appendicitis from that due to distention of a hollow viscus, such as the gall-bladder or pelvis of the kidney, which soon reaches its maximum and continues with constant severity until it subsides spontaneously or is relieved by morphin. When there is marked distention of the appendix the pain may be excruciating and the temperature low. The pain may subside or be greatly relieved if perforation occurs. This relief was frequently regarded as evidence of improvement before the true character of appendicitis was recognized.

Localized Tenderness and Rigidity Over the Appendix.—Early in the disease a definite localized tenderness develops over the appendix (*McBurney's point*), usually at the middle of a line joining the navel and the right anterior superior spine. Definite muscular rigidity is also noted; indeed, the muscular spasm may be so severe as to produce a ridge in the abdominal wall. This tenderness and rigidity may develop in other positions, depending upon the location of the appendix: when this organ is retrocecal they may be noted posteriorly. The rigidity (muscular defense) is usually so great that palpation of the right iliac fossa is difficult or impossible. It is so marked that it is rarely misinterpreted after being once encountered. Localized tenderness, associated with the muscular rigidity, is one of the most important signs of appendicitis.

Temperature.—Appendicitis rarely begins with a chill, and at the be-

ginning or during the course of the disease this symptom is suggestive of some complication, such as suppurative thrombosis of the portal vein (pylephlebitis). The temperature curve is neither typical nor characteristic. It is sometimes difficult to determine the exact variations in temperature, for often the surgeon sees the patient only after fever has developed, or when removal of the inflamed appendix has modified the temperature. Appendicitis is never absolutely fever free. The temperature may vary from 99° or 99.2° to 103° F. or more. The fever is more often low or moderate than high. It may continue for different lengths of time, subsiding after one or two days, or persisting for a week or more with evening exacerbations. Naturally, the character of the fever and its duration are modified by the formation of abscesses. It is well when there seems to be no fever to take the temperature by rectum, because even when the mouth temperature is normal, the rectal temperature may be elevated.

Leukocytosis.—A white blood-cell count varying from 10,000 to 35,000 may be regarded as confirmatory of the clinical manifestations. In some exceptionally severe infections which cause gangrene and a spreading peritonitis there may be no leukocytosis because of a reduction in the defense mechanism. Leukocytosis is of considerable importance in distinguishing between the type of typhoid fever which begins with abdominal pain and appendicitis. In the writer's opinion, too much importance is sometimes placed upon leukocytosis and its differential significance. The clinical symptoms must always be the basis of diagnosis, and leukocytosis should be considered merely confirmatory and helpful. The degree of leukocytosis does not characteristically vary with the different types of appendicitis. While a decrease in the number of white blood-cells probably indicates improvement, the clinical symptoms must be carefully reviewed before this is assumed.

Vomiting is so inconstant that it probably should not be regarded as a symptom of appendicitis. It is incidental. Some patients are not even nauseated, while others have severe and protracted vomiting. It has been said that more or less marked *constipation* is invariably associated with appendicitis, but there may be no gastro-intestinal symptoms. Among the 50 cases carefully observed by Treves constipation was noted in 26; diarrhea, in 13; normal movements, in 8; and constipation alternating with diarrhea, in 1. While constipation or normal movements are observed in the majority of cases, appendicitis not infrequently begins with severe diarrhea. Cramp-like abdominal pains associated with diarrhea may cause some difficulty in diagnosis. Localized tenderness and rigidity are most important diagnostic signs.

Complications.—Abscesses and Spreading Peritonitis.—As a result of perforation or gangrene of the appendix the inflammatory process may extend to adjacent tissues (perityphlitis) and become localized, or it may involve the peritoneum more or less completely. If an abscess forms, the fever continues, with more or less marked evening exacerbations; a tender mass can be palpated; and usually a decided swelling is seen at the site of the abscess. In diffuse spreading peritonitis the Hippocratic facies is noted, the abdomen is distended, and paralytic ileus develops. A peculiar black fluid, the so-called *fecal vomitus*, runs out of the mouth or is vomited in large quantities, and the hands and feet become blue and cold. In

general peritonitis the mouth temperature may be low, but the rectal temperature 108° F. or more.

Suppurative Thrombosis of the Portal Vein (*Pylephlebitis*).—It is difficult to determine the frequency with which suppurative thrombosis of the portal vein occurs. It may develop during the first attack or during recurrences. The writer has observed a case of suppurative pylephlebitis, symptoms of which developed twenty-four hours after the removal of a gangrenous appendix. In another instance, the patient had a distinct chill at the beginning of the fourth recurrence and subsequently died of suppurative pylephlebitis. Chills and fever suggest this complication. The liver becomes enlarged and tender. Jaundice or a subicteric tint is noted. Later there may be some ascites. Aspiration of the liver at operation may reveal pus, but often none is found. Miliary abscesses may be present.

Subphrenic Abscess.—The inflammatory process, especially if the appendix is retrocecal, may extend upward and, by involving the right subphrenic space, produce a right subphrenic abscess. The temperature then continues high, and a dulness extends high up on the chest; the liver may be displaced downward, and the *x*-ray reveals a high diaphragm and, in some instances, gas between the diaphragm and liver. Aspiration reveals pus.

Pulmonary Embolism.—Embolism of the lungs with infection is seen occasionally. The clot forms in the veins of Retzius or in the veins of the pelvis or extremities. In some cases the vein is probably infected by the appendix which lies close to it. If a large clot forms, death may take place almost instantaneously, but small clots give rise merely to pain and bloody expectorations. A friction-rub develops over the area involved and an effusion forms which remains hemorrhagic or becomes purulent, according to the number and variety of the infecting organisms.

Hemorrhage from the Stomach.—Emboli may lodge in the stomach and cause considerable hemorrhage. Eiselsberg, who lays special emphasis on this complication, noted several cases of hemorrhage from the stomach, most of which occurred after appendectomy, and should probably be considered as a *postoperative* complication. The hemorrhages, according to him, were due to the lodgment of emboli and were associated with some ulceration. Hildebrandt reports a case of severe acute hemorrhagic nephritis which developed thirty-six hours after the onset of acute appendicitis. This suggests embolism.

Diagnosis.—Renal and Ureteral Calculi.—Colic due to renal and ureteral stone must be considered very carefully in the differential diagnosis. If the ureter is involved in an inflammatory process because of contiguity of an inflamed appendix, red blood-cells and even macroscopical blood may appear in the urine. Differentiation between a ureteral stone and acute appendicitis may be quite difficult. The pain associated with renal and ureteral stones tends to become maximal soon after the beginning of an attack and to maintain this severity without much variation; while that of appendicitis is distinctly intermittent, and undergoes distinct exacerbations due to peristalsis. This characteristic is often of great value in making a differential diagnosis. The radiation of the pain caused by renal and ureteral stones is quite characteristic, and the definitely localized tenderness of appendicitis does not, as a rule, accompany the disturbances produced by either renal or ureteral stones. Although in the latter case there is

often tenderness, it is not associated with the distinct characteristic muscular rigidity. An *x*-ray examination will determine the presence or absence of stone.

Intermittent hydronephrosis may simulate appendicitis. The pain usually reaches its maximum level, and remains there without exacerbations. The enlarged kidney may be palpated. The pain radiates into the groin or downward. It may be dull and felt mostly in the flank. A large quantity of urine may be discharged after the obstruction is overcome. A pyelogram will permit differential diagnosis.

Gall-stone colic begins with epigastric pain, which radiates to the back if the stone reaches the pelvis of the gall-bladder or the cystic duct, and seems to pass directly through the body to the angle of the scapula. A history of repeated attacks, some of which may have been associated with jaundice, tenderness in the right hypochondrium, and usually rapid recovery from the pain, aid in making the diagnosis. Since the gall-bladder may be in the region of the appendix when the position of the liver is low, the localized tenderness during an attack of gall-stone colic may lead one to suspect appendicitis.

Duodenal Ulcer.—A chronic history with recurrence of acute symptoms is characteristic of duodenal ulcer. In duodenal ulcer a history of hunger pains and pain which comes on at night and is relieved by soda or food can usually be elicited. The pain associated with rupture of an ulcer develops suddenly, is excruciating, and is usually accompanied by some degree of shock. Grunting respiration is usually noted and the board-like rigidity of the upper part of the abdominal muscles on the right side is very suggestive. The duodenal contents poured out into the abdomen gravitate along the outer side of the colon toward the right iliac fossa, and some hours after perforation distinct tenderness and rigidity may be found over the appendix. The previous history aids diagnosis.

Acute salpingitis should be suspected if there is a vaginal discharge and pain low in the abdomen or at the brim of the pelvis. A pelvic or rectal examination should be made. In the cases of acute appendicitis in which the appendix lies in the pelvis it may be difficult or impossible to differentiate between an abscess developing from the tubes and one from the appendix.

Strangulation of the Pedicle of a Uterine Fibroid or Ovarian Cyst.—The pain produced by strangulation of the pedicle of a uterine fibroid or ovarian cyst is usually different from the peristaltic pain associated with appendicitis. Localized tenderness and rigidity are usually present, but are situated where the tumor comes into contact with the parietal peritoneum. The tumor can usually be palpated.

Prognosis.—The prognosis depends entirely upon whether the appendix is removed early in the attack while the inflammatory process is localized, or whether operation is postponed until the appendix has ruptured and peritonitis, local or diffuse, has developed. If the appendix is not removed before the inflammatory process has extended to the peritoneum, the mortality varies considerably, and depends upon the character of the infecting organism and the extent to which the peritoneum is involved. When the appendix is removed soon after the beginning of the attack the prognosis is excellent. It is difficult to determine the mortality, but it is extremely low, and death is usually due to some surgical accident, such as hemorrhage from the stump of the appendix, embolism, or peritonitis.

If, however, peritonitis or a subphrenic abscess has developed, the mortality may be extremely high.

Treatment.—Appendicitis demands immediate *surgical treatment* because the symptoms do not indicate the exact character and progress of the lesion and because the appendix should be removed if possible while it alone is the seat of the inflammatory process. When performed during the early stages appendectomy is followed by as prompt recovery as when the appendix is removed during the interval between attacks. In some cases when the patient is seen from three to four days after the beginning of the attack, it may be a question whether it would not be better to delay operation until resolution has occurred or an abscess has formed. The decision must rest with the surgeon.

Cathartics should not be given at the beginning of an attack. Morphin should be administered to control peristalsis after the diagnosis is made, never before. Nothing should be given by mouth. Every attempt should be made to limit the spread of the inflammation. This is accomplished largely by controlling peristalsis as much as possible.

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APPENDICITIS IN CHILDREN

Bolling states that after the first year of life appendicitis is the most common of all the acute abdominal diseases. In a series of more than 16,000 cases in children compiled by Kelley, 2.5 per cent. occurred during the first five years of life; 8.3 per cent., during the second; and 16.3 per cent., during the third. The symptoms of acute appendicitis in children are the same as those observed in the adult, but are not always so definite. Diagnosis may, consequently, at times present certain difficulties. The pain which initiates the attack may be indefinitely localized and the physician may have to be content with the statement that the child seemed to have the cramps. In the adult *pressure* usually increases the tenderness and discomfort, while in children abdominal massage at times alleviates the pain even in acute appendicitis. *Vomiting* is noted with far greater regularity in children than in adults. As in the adult, constipation is more common than diarrhea. If considerable mucus is present in the stools a diagnosis of *dysentery* is sometimes made. *Fever*, *tenderness* and *rigidity*, and *leukocytosis* are present regularly. It should, however, be remembered that the rigidity is neither so constant nor so marked as in the adult. As it is often detected with difficulty, light pressure should be used when attempting to determine its presence. Though muscular rigidity may not be present to any marked degree, tenderness is as characteristic as in the adult. While the diagnosis of appendicitis in children, especially in those less than two years old, offers some difficulties, it is made more and more frequently, for we now know that it is not an uncommon lesion even at this age. Acute appendicitis in children, particularly in babies two years of age and under, tends to run a severe course, for the inflammation is usually less localized and peritonitis is more frequent and wide-spread than in older children and

adults. The omentum which at this period of life is not fully developed cannot wall off the inflammatory focus and protect the peritoneal cavity as it does in the adult. The immunity is also less than in later years. In considering the differential diagnosis, mention should be made of *lobar pneumonia* with referred abdominal pain. The chest findings may not be definite and the referred pain may be confusing. The abdominal pain and tenderness, however, are more general than in appendicitis and are higher in the abdomen. The tenderness associated with pneumonia is so superficial as to suggest cutaneous hyperesthesia, and usually is not increased by deep palpation. Diagnosis must be based upon a carefully elicited history and the signs already mentioned. It should be kept in mind, however, that abdominal pain may occur in children with a number of lesions unassociated with any evidence of distinct abdominal pathology. It has been noted with *measles, throat infections, osteomyelitis of the femur, inguinal* and *femoral adenitis*, etc.

Intestinal parasites must be mentioned in a consideration of the etiology of appendicitis in children. They are occasionally encountered in the adult. Cecil and Bulkley have discussed the relation of *Oxyuris* and *Trichocephalus trichiura* to the disease. Many believe that the *Oxyuris* plays no etiological rôle and that its occurrence in the acutely inflamed appendix is merely accidental. Cecil and Bulkley found this parasite in 15 out of 40 cases of non-suppurative appendicitis. It is, however, also found in apparently normal appendices, in the submucosa as well as in the lumen. Often little or no inflammatory reaction is found about the oxyuris, but while it may be impossible to demonstrate the point at which the organisms penetrate the mucosa, they are supposed to produce characteristically shallow hemorrhagic ulcers in the mucosa. These might be the starting-point of an acute inflammatory process not unlike that described by Aschoff in the adult appendix. Parasites are not nearly so common in the suppurative and gangrenous forms of appendicitis as in the non-suppurative type.

The high death rate among children with appendicitis is in some measure due to late recognition of the disease. Cathartics should not be given until the possibility of appendicitis is excluded. When the diagnosis is made, surgical intervention is indicated. If the appendix is removed when the inflammatory process is confined to it, the prognosis is excellent. The failure to recognize the disease before a diffuse or general peritonitis has developed is partially responsible for the high mortality in children.

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CHRONIC APPENDICITIS

The term "chronic appendicitis" has been applied indiscriminately and promiscuously to a number of lesions and symptoms which have no relation whatsoever to the appendix. It should be applied only to those changes which persist after an acute attack. In discussing the etiology of acute appendicitis it was stated that in almost 70 per cent. of the cases repair of the changes associated with the first attack produced alterations which predisposed to a recurrence of an acute attack. Such changes may be stenosis

of the lumen of the appendix following healing of an ulcer, or obstruction of the lumen by kinks or bands after a peritonitis. Interference with the function of the appendix may give rise to indefinite symptoms often referred to an organ at a distance, accompanied by definite localized tenderness and more or less discomfort. The lesions and symptoms which persist or develop after an acute attack fall under the heading of chronic appendicitis. Because of the frequency with which an acute attack supervenes in such cases the term "chronic recurring appendicitis" is probably more appropriate.

The symptoms of chronic appendicitis following recovery from an acute attack are frequently referred to the stomach and intestines, and in many cases it is difficult for the patient to describe definitely the symptoms or to give an exact location of the distress. There may be loss of appetite, a sense of fulness after eating, and pain and tenderness in the epigastrium, symptoms usually associated with lesions of the stomach. The somewhat unfortunate term "*appendicular dyspepsia*" was introduced by Longuet to describe these symptoms. In another type of the disease the symptoms are most pronounced in the lower abdomen—more or less tenderness, sometimes diffuse, more often localized over the site of the appendix, constipation, and some irregularities in digestion. Tenderness, with aggravation of symptoms, is often noted after bending, or lifting, or carrying a load. The indefiniteness of the symptoms often renders diagnosis of chronic appendicitis difficult, but with the history of a previous acute attack followed by persistence of more or less localized tenderness and the development of the rather indefinite syndrome described above true chronic appendicitis should be recognizable.

Typhlocolitis.—Not infrequently relief fails to follow removal of the appendix for so-called chronic appendicitis, typhlalgia, cecum mobile, and Jackson's membrane; and often in such cases no pathological changes can be discovered in the appendix itself. Dieulafoy, an advocate of the early surgical treatment of acute appendicitis, was one of the first to point out the possibility of confusion with *mucous typhlocolitis*. In 1906 he published reports of 35 cases in which such an error had been made, and emphasized the diagnostic importance of examination of the stools. He states that when a membrane or intestinal sand is found in the stools during an attack there can be little possibility of appendicitis. Glenard describes similar conditions as *typhalgia* and considers them to be due to mechanical obstruction in the hepatic flexure. Much the same syndrome has also been ascribed to the obstruction produced by bands of adventitious tissue or to traction upon a membrane first described by Jackson (*Jackson's veil* or *membrane*). None of these conditions are related to chronic recurrent appendicitis, and the symptoms are not, therefore, relieved by appendectomy.

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INTESTINAL OBSTRUCTION

The term "intestinal obstruction" is in itself a sufficient definition. Hemmeter, Nothnagel, and others prefer the appellation "intestinal occlusion" as being more inclusive. Hemmeter differentiates and defines the various occlusions as follows: "Stenosis: A narrowing of the intestinal lumen. Occlusion: A closure, blocking, or shutting up of the bowel. Stricture: A reduction of the lumen of the intestine by circular internal disease of the intestinal wall. Constriction: A narrowing of the intestinal lumen from the circular binding effect of external causes. Obturation: Closure of the lumen by impediments within the intestinal canal. Intussusception: An invagination or telescoping of one part of the intestines into another."

Nothnagel further differentiates intestinal obstructions as "mechanical, dynamic (paralytic), and mechanico-dynamic." Intestinal obstruction may be acute, recurrent, or chronic. Depending on its cause and its degree, it may be partial or complete.

Etiology.—Among the many causes of intestinal obstruction are such common conditions as *strangulation*, *twists*, *kinks*, *knots*, *intussusception*, and *occlusion by abnormal contents*, *strictures*, and *tumors*. Since the etiology is so varied, the relative occurrence of the different causes is best shown in tabular form. The findings of Fitz, Leichenstein, Brinton, and Hemmeter are combined in Table I. Each cause included in the table will be separately discussed.

TABLE I

Causes of Intestinal Obstruction

	Number of cases.	Per cent. caused by:				
		Strangulation.	Intussusception.	Twists and knots.	Abnormal contents.	Strictures and tumors.
Fitz	295	34	32	14	15	5
Leichenstein	1134	35	39	6		
Brinton	481	33	54	10		
Hemmeter	500	38	33	16	9	4

Strangulation, the most frequent cause of acute obstruction in the adult, results from anatomical abnormalities such as adhesions, Meckel's diverticulum, adherent appendices, mesenteric and omental slits, peritoneal

pouches and openings, an adherent tube, and pedunculated tumors. The condition, according to Fitz, is somewhat more common in males than in females and is rare in early youth. After the age of thirty adhesions are the most usual cause.

Intussusception is the invagination of one section of intestine (the intussusceptum) into the section next below (the intussuscipiens). The ascending type is very rare. The small intestine alone (enteric invagination) or the colon alone (colonic invagination) may be involved, or the small intestine may become invaginated by the colon (ileocecal invagination). The condition is most frequently seen in infants and children. Gibson states that 72 per cent. of his cases occurred in males.

Transient intestinal invagination may be a peristaltic phenomenon. According to Nothnagel and others the pathological type is caused by pulling up of a section, usually by the longitudinal muscle-fibers, about a spastic zone just above. Paralysis of the lower section is not considered a common cause. Among the other etiological factors are imbalance of intratubular tension and polypoid growths, cancers, foreign bodies, and Meckel's diverticulum, which have been known to drag a section of intestine into an invagination.

Volvulus.—Twists, kinks, and knots are not to be confused with strangulation due to bands, slits, or pouches. They are caused by a twisting of the intestine upon its mesenteric axis, which occludes the lumen. *Congenital irregularities* in the length of the mesentery, or of the intestine, or an acquired redundancy of the tube, promoted by constipation, may be etiological factors. *Trauma*, the result of falls, jumps, or other physical shocks, also produces many such accidents, as well as violent catharsis or any agent that induces overactive peristalsis. The weight of a fecal mass or tumor, extratubular pressure, rough manipulation of intestinal tissue during laparotomy, and paresis of the intestine after surgical treatment, are all reported to play a causative rôle.

Volvulus occurs most frequently in males of middle age. In 50 per cent. of patients the sigmoid flexure is involved. The site next most frequently attacked is the ileocecal region. The small intestine is affected in about 13 per cent. of cases.

Strictures and Tumors.—Stricture of the intestine may be the result of some *congenital defect* or of *inflammatory changes* (the ulcerations of dysentery, tuberculosis, and syphilis) in the intestinal wall. Examples of this are given by Solieri, who observed that undue shortening of the ileocecal fold brings the terminal portion of the ileum so close to the cecum that an acute angle is formed which obstructs in some measure the flow of fecal matter. *Extratubular pressure* exerted by masses of adhesions (pelvic abscesses, peritonitis) also causes stricture; and large tumors, cysts in adjacent structures, and even the gravid uterus have been thought to exert a similar effect. Intestinal *tumors*, both benign and malignant, which are among the common causes of obstruction, will be discussed in a separate section.

Abnormal Contents.—Of the many foreign substances and structures which have been found to obstruct the bowel, it is worth while to mention only large gall-stones that have ulcerated through the gall-bladder into the intestine, hair-balls, round worms in masses, coins, jewelry, enteroliths, impacted feces, and the barium sulphate used for *x*-ray purposes which

occasionally becomes hard and causes intestinal impaction, usually in the pelvic colon.

Paralysis of the Intestine.—Spastic occlusion and dynamic ileus are relatively rare. The paralytic condition may follow occlusion of the blood-vessels supplying a section of intestine, and at times result from mesenteric thrombosis or embolism. Paresis of the intestine may be produced by the constitutional changes due to acute infection, surgery, shock, and traumatism. Perhaps the most frequent cause of all is acute peritonitis.

Symptoms.—By experiments, complete intestinal obstruction has been proved to occur without producing any of the symptoms commonly associated with it. When the strictures and occlusions form slowly this has been observed many times. Such lack of symptoms is more often noted with fecal impactions or occlusions not accompanied or complicated by inflammatory changes in the involved parts.

The severity of the symptoms seems to be definitely related to the degree of damage in the walls of the tube and the adjacent mesentery. Consequently, the most pronounced early symptoms are associated with strangulation, intussusception, and volvulus.

Acute Intestinal Obstruction.—*Pain.*—A sudden tearing or cramp-like abdominal pain is usually the first symptom. In the early stages it may be circumscribed and roughly restricted to the site of the obstruction, but it rapidly spreads over the abdomen. Such pain is usually referred to the midabdomen and is not always continuous. It may diminish in severity from time to time, only to recur with increased intensity. When the small intestine is obstructed the waves of pain are more frequent and intense than when the colon is involved. Sudden cessation of pain with continuance of other symptoms is of serious import. The sleep induced by opiates is not one of repose; the pain frown remains. Mutterings and restless movements indicate that the agony is only partially numbed. While at first the pain may be relieved slightly by pressure, as peritonitis develops (as it does sooner or later in most cases) the whole abdomen becomes so sore that the pressure of the lightest clothing or bed covering is intolerable.

Vomiting begins soon after the onset of pain, and is at first entirely reflex. The previous meal is often thought by the patient to be the cause of trouble. When the stomach is empty only bile-stained gastric juice may be expelled, or the patient may be convulsed by unproductive retching. Each spasm of pain culminates in an attack of vomiting. Not long after onset a glairy, smooth, gray material is raised; but if the obstruction is low such vomitus may not appear for hours. In a case recently observed by the writer this substance was not vomited until seventy hours after the onset, and the obstruction was found at autopsy to be in the ileocecal region. When this material, which is the characteristic content of the small intestine, is raised, the type of vomiting usually changes. Although it probably continues to be in part reflex until the end of most attacks, the intestinal contents seems to be propelled to some extent by the strong gas pressure that develops proximal to the obstruction. This is evidenced by the explosive character of the discharge. Gradually, however, much of the explosive force seems to diminish, and the characteristic vomitus is gulped up almost continuously. At first this smooth gray material smells only faintly of moldy food, but after a few hours the odor becomes slightly fecal. This stercoraceous vomiting is not necessarily a sign that colonic

contents are present in the vomitus. The contents of the small intestine (particularly the albumins) which normally passes rapidly through this portion of the tube, putrefies quickly when impeded in its progress and produces the fecal odor. The gray material which may contain little or no food consists for the most part of pancreatic and intestinal secretions. Secretion is stimulated by the splanchnic irritation and circulatory stasis. The vomitus contains little bile because the gall-bladder has usually been emptied by the retching of the initial reflex vomiting. Stercoraceous vomiting is the most characteristic symptom of intestinal obstruction.

Distention (Meteorism).—In only a few cases of intestinal obstruction is abdominal distention not a marked feature. At onset its more or less definite localization may permit determination of the approximate location of the obstruction by inspection and percussion; but as the muscularis becomes paralyzed, as it almost invariably does, the distention becomes diffuse, until the abdomen assumes the characteristic barrel shape. Such paresis of the intestinal muscularis must for the most part follow damage to the circulation of the tube, since when obstruction is due to impaction which produces little or no such injury, distention is absent or relatively slight. Meteorism is the direct result of fermentation of the intestinal contents during stasis. If the blood-supply of the intestines is unimpaired, large quantities of gas are rapidly absorbed by the blood, but if the vascular apparatus is deranged, enormous quantities may accumulate.

When the obstruction is high in the tube (duodenum or jejunum) the distention is confined to the upper abdomen until the late stages of the disease. Under such conditions the gas is easily discharged during vomiting unless the stomach muscles are involved in the acute atonia. This occasionally happens in high duodenal occlusions caused by constriction of an angiomesenteric band (Harris band). Acute dilatation of the stomach may be brought about by such an accident.

Shock.—Some degree of shock or collapse is noticeable in all patients with acute intestinal obstruction in which the walls of the intestines or the mesentery are damaged by constriction, strangulation, incarceration, twists, and knots. This symptom depends on the circulatory imbalance caused by the vasomotor paralysis incident to severe splanchnic irritation. The abdominal viscera become engorged with blood drawn from the rest of the body.

Shock is evidenced by the small, rapid pulse, subnormal surface temperature, extreme prostration, pallor, and sweating. The skin is cold and clammy, the respirations short and superficial. The anxious, pinched facies is quite distinctive. The patients seem to know instinctively that they are stricken.

Other Symptoms.—The voice is husky. Dehydration results from the continuous vomiting and sweating, and produces the intolerable thirst and thick brown tongue.

The urine may be diminished or lacking. Albumin is commonly present in the *urine* and the indican content is characteristically increased, particularly when the stoppage is in the small intestine. If the quantity of indican is not increased, the obstruction is more apt to be in the colon, but after an acute colonic obstruction has persisted for several days indicanuria may be pronounced.

The *blood* nitrogen content is increased in high obstructions. The leukocyte count usually rises during very acute obstructions.

The *bowels* do not usually move spontaneously after an acute attack, although the material in the tube distal to the occlusion may be discharged in one or two spontaneous movements. An enema may induce a small movement. If the occlusion is not complete, small diarrheic movements usually occur. Blood may be passed after strangulation. Intussusception is characterized by frequent passage of small amounts of blood and mucus. Flatus is rarely passed when the obstruction is complete.

Chronic Intestinal Obstruction.—Slowly developing and chronic obstructions, particularly those dependent on the stenoses of neoplasms, produce symptoms quite different from those of the acute occlusions. *Constipation* is usually the first manifestation noted. It may be only relative, the movements being smaller than normal and not followed by a feeling of relief, or more frequent than usual, and soft and spurty in character. The slight colicky *pains* which soon develop throughout the abdomen may be relieved temporarily by a discharge of flatus, but continue to increase in severity at each recurrence. They are increased by laxatives, but, if the bowels move, relief may continue for many hours or even days. Without surgical treatment this syndrome becomes similar to that characteristic of the late stages of acute obstruction. Fecal impaction, which often exists for a considerable time in the aged without causing symptoms, is suddenly manifested by profound *shock*. Tunneling of an impaction has been known to take place. In such cases the symptoms of obstruction may be lacking or appear in recurrent attacks. The sudden development of hemorrhoids in an elderly person demands digital examination of the rectum, for they are frequently caused by impaction.

Very interesting are those recurrent partial occlusions of the duodenum seen in poorly developed young people. Angiomesenteric bands (Harris bands) not infrequently embarrass the duodenum of these physically inferior individuals. The occlusions may occur in recurrent attacks, the attacks being dependent on sudden loss of gastric tonus because of fatigue, emotional excesses, or constitutional causes; or through traction of the mesocolon on the angle of Treitz a partial stoppage in the duodenum is effected. An overloaded colon may provoke this, or in some such cases loss of colonic tonus with sudden ptosis will act likewise. The attack is not unlike migraine. First, a loss of appetite with headache; this culminates in vomiting, the vomitus consisting of large quantities of bile-stained watery material. Through fasting, rest in bed, and a laxative, relief is obtained after one to four or five days.

Physical Signs.—Very early in *acute intestinal obstruction* a localized *distention* may be observed. That of the small intestine is frequently evident in a "ladder pattern"; that of the colon, in a "horseshoe pattern." The peristaltic movements which are rarely visible in such cases can at times be seen to be toward the obstruction. Visible peristalsis, however, is much more characteristic of chronic or slowly developing obstruction. If the bulging is in the upper abdomen while the lower quadrants are relatively retracted, the trouble may be assumed to be in the upper small intestine. Distention of the lower right quadrant suggests that the lesion is in the ileocecal region. An obstruction in the sigmoid should cause bulging of the lower left quadrant. If an initial pain corresponds to such localized distention, the obstruction is presumably not far from the place of bulging. It is rare, however, for a physician to examine the patient so early that this

localized distention can be seen; generalized distention is not slow in developing. In the obstructions it is difficult to differentiate the sense of resistance caused by gas distention from that of the abdominal muscles. Its character is quite different from the board-like resistance associated with perforated gastric ulcer, acute pancreatitis, or mesenteric thrombosis. The extreme distention and abdominal tenderness seldom permit palpation of an abdominal mass, although this is occasionally possible in intussusception, fecal impaction, or the stenoses of neoplasms when the distention is not extreme. By digital exploration of the rectum or vagina the rounded head of an intussusception may occasionally be felt. The inguinal rings should not be neglected in such examinations.

The careful use of the stethoscope over the abdomen occasionally helps in locating the site of an occlusion. Shrill whistles or muffled, bubbling sounds, which continue in one spot, are significant.

If the patient is in a hospital equipped with a portable *x*-ray apparatus several films of the abdomen should be taken at the earliest opportunity Barium or any other contrast material should, of course, be avoided. The characteristic shadows of gas collections thus made evident are often sufficient to confirm diagnosis, and to locate accurately the site and character of an obstruction. The procedure taxes the patient but little.

Diagnosis.—The successful treatment of *acute intestinal obstruction* demands early, accurate diagnosis. The treatment is surgical, except rarely in low impactions and low intussusceptions, and there is seldom time for leisurely observations. The first question to decide is whether an obstruction is actually present, or whether the lesion is inflammatory and amenable to non-surgical treatment. In typical cases this should not be difficult. Shock, increasingly severe abdominal pains, stercoraceous vomiting, distention, and obstipation should automatically determine diagnosis.

The character of the onset is of prime importance. The sudden beginning of intense pain, with vomiting, and early, profound collapse is evidence of acute stoppage in which the intestinal tube has been severely pinched, squeezed, or strangulated, with resulting disturbance of its blood and nerve supply. Strangulations, incarcerations, invaginations, twists, and knots are the most probable causes of such a condition, while strictures, obturations by foreign bodies, or impactions generally produce symptoms more gradually and are often associated with a suggestive history—similar previous attacks, alternating constipation and diarrhea, loss of weight, and anemia. The age of the patient helps somewhat in this differentiation: intussusception is largely a disease of infancy and young childhood; twists and knots, and also strangulations and incarcerations, are more common during and after middle age. The pain caused by an intussusception is usually paroxysmal; and the condition is characterized by considerable tenesmus and frequent evacuation of small quantities of blood-streaked mucoid material at the onset. A small, hard, movable, tender tumor can occasionally be felt in intussusception. This is not infrequently present in the pelvic colon and can be reached by the examining finger through the rectum. In a healthy baby the sudden onset of these symptoms with shock is diagnostic.

The syndrome of *obstruction* by *foreign bodies and impactions* begins more gradually and is constituted of symptoms which are rarely as severe or as characteristic as those of other forms of obstruction. Distention may be entirely lacking until the very late stages. A large, moderately soft

mass which represents the impaction may be palpable. When an impaction or stricture has been developing for considerable time, compensatory hypertrophy of the intestine proximal to the obstruction may cause visible peristalsis, particularly when an incomplete stenosis has made impaction possible. Visible peristalsis is characteristic of slowly developing and of *chronic obstructions.* The obturations are most frequent in middle-aged and aged patients, although young children and the insane of all ages are prone to swallow obstructing foreign substances. Nearly all obstructions by gall-stones occur in middle life or old age, usually after repeated attacks of gall-stone colic. There is rarely any difficulty in diagnosing chronic obstructions. The *x*-ray is indispensable in determining the exact location of the lesion and its character.

Certain abdominal diseases may produce syndromes quite similar to those of intestinal obstruction. *Acute peritonitis* is usually distinguishable because it is preceded or accompanied by the disease which plays an etiological rôle, and also because fever is associated with its onset, and is not one of the symptoms which develops late, as in intestinal obstruction. The abdomen is more tender in peritonitis, and the pains tend to decrease, while in obstruction they increase. In peritonitis, stercoraceous vomiting occurs only when the intestine becomes occluded by paralysis. If this takes place the symptoms are those of obstruction plus those of peritonitis. The passage of gas and feces is possible in peritonitis, rare in obstruction.

Acute food poisoning (severe acute infectious gastro-enteritis) may at first be responsible for symptoms not unlike those of acute intestinal obstruction. The diarrhea is an aid to differentiation. Distention is not common, the collapse not so marked. The vomiting is never stercoraceous.

Acute cholecystitis, acute cholelithiasis, acute appendicitis, acute inflammatory disease of the female pelvis and the genito-urinary tract, acute perforations, mesenteric thrombosis, and *acute pancreatitis* are all to be differentiated.

It is well to remember that the local or general peritonitis which may complicate any of these inflammatory abdominal diseases may confuse the syndrome by producing paralytic ileus.

Prognosis.—*Intussusception* is occasionally followed by complete spontaneous recovery when the mesentery which is dragged into the invagination is not damaged. In the few cases in which the invaginated section of the intestine has undergone necrosis, sloughed off, and been evacuated through the rectum, the outer layer (the intussuscipiens) attaches itself in a ring about the invaginated section to form a complete, permanent joint. *Twists, kinks,* and *knots* have been corrected spontaneously or by postural treatment and massage. When an obstruction has been sufficiently acute and severe to cause shock and stercoraceous vomiting, it is doubtful if the patient can recover without surgical treatment. The hope of cure by surgery diminishes with each hour that such treatment is withheld. If acute obstruction goes untreated the patient dies within a few hours to ten days.

The prognosis in *chronic obstruction* depends largely upon the cause. The partial and recurrent occlusions caused by bands or by kinks due to lowered tonus of the abdominal structures appear to be relieved considerably by orthopedic treatment. Some patients recover completely. Surgery should not be employed in these cases before a more conservative plan of treatment has proved ineffective.

Treatment.—For *acute obstruction* prompt surgical measures are nearly always necessary. Should the cause appear to be a low fecal impaction, every effort should be made to give relief by careful rectal washing and digital or instrumental excavation. When the intussusception is low enough to be felt by rectal examination, it is well to *distend the colon* with water and to give *postural treatment* unless the trouble has existed for any length of time, or unless there is marked and continuous discharge of blood. Such treatment should not be employed in the other forms of obstruction, particularly in those which produce extreme symptoms like profound shock. *Lavage* is desirable when there is gastric dilatation or incessant stercoraceous vomiting. In most cases water may be introduced into the rectum by the Murphy drip method or administered by hypodermoclysis. Nothing should be given orally, but the mouth should be constantly moistened. *Purgatives* should not be given. *Morphin* is valuable before operation or when the outcome is obviously fatal, but must not be administered until after diagnosis is certain. *Belladonna* and *atropin* are worthless when the condition is severe. *Digitalis* ought to be given as a routine procedure. *Adrenalin* is of questionable value, and *strychnin* useless. *Hot fomentations* give some comfort.

Chronic intestinal obstruction also usually requires surgical therapy except when fecal impactions can be reached by enemas. *Instillations of warm oil* help soften such feces, and instillation of a dilute solution of *peroxid of hydrogen* sometimes tends to disintegrate hard, impacted material. The *diet* should be as concentrated as possible. Administration of the various emulsions of *mineral oil* with agar should be tried, or plain mineral oil, or chemically pure vaselin. While laxatives are usually to be avoided, *cascara* may be used with care in some cases.

Arthur L. Holland.

INTESTINAL NEOPLASMS

Malignant Growths.—Incidence and Etiology.—Neoplasms of the intestines are of relatively high incidence. Ewing, quoting many authorities, gives the following statistics: "Of 22,340 cases (German sources) 8.56 per cent. were intestinal. Of 52,420 deaths from cancer (U. S. Census, 1914) 11.8 per cent. were of the peritoneum, intestine, and rectum. It is rare in the duodenum. Ten cases have been reported in what appeared to be the scars of duodenal ulcers. In the ileum and jejunum its incidence is approximately 3 per cent. of all intestinal cancers. Of 2,336 cases of intestinal cancer, the appendix was primarily involved in 0.39 per cent. (probably too low an estimate). Of 297 cases of cancer of the colon, 47 were in the cecum, 22 in the ascending colon, 19 in the hepatic flexure, 44 in the transverse colon, 31 in the splenic flexure, 10 in the descending colon, and 124 in the sigmoid. Sixty per cent. of intestinal cancers occur in the rectum. 5.25 per cent. of all cancers are rectal."

The anatomical arrangement of the intestine in which histologically

different structures are placed in near contact, the richness of its glandular equipment, its unusual exposure to trauma and parasitic irritation, and its proneness to ulceration with consequent cicatrization, all probably play a part in the etiology of intestinal neoplasms.

Sex and Age.—Of 6,330 cases (U. S. Census, 1914) 2,690 were in males, 4 in infants under one year, and 19 under five years. The highest incidence was between sixty and sixty-five years. Cancer of the small intestine and of the appendix seems to occur earlier; there are many of these cases reported in patients under forty; not a few were under thirty years.

Morbid Anatomy.—The morbid anatomy of cancer of the first portion of the duodenum is identical with that of cancer at the pylorus. In the second portion the growths are usually papillary in origin, although some extend along the intestine and involve the biliary papilla by extension. The few cases of cancer of the third portion reported have been of stenosing cylindrical-cell adenocarcinomata. Most cancers of the intestines are adenocarcinomata. In the small intestine, they rarely develop from a polyposis, but usually originate in a single adenomatous polyp. Gelatinous adenocarcinomata have been found in the small gut and in the appendix. The spheroidal-cell alveolar carcinoma occasionally found in the appendix is benign and occurs early in life. Ewing describes 7 varieties of cancer in the colon and rectum: adenoma distruens (the most typical); stenosing fibrocarcinoma; gelatinous adenocarcinoma; carcinoma developing from solitary polyps; intestinal polyposis; squamous-cell carcinoma (lower rectum); and melanoma. Most of the sarcomata found in the intestines are lymphomatous, although spindle-cell myxosarcoma is occasionally found in the cecum and appendix. Melanosarcoma is relatively rare. Sarcoma rarely causes stenosis; its growth is along the intestinal wall and out. It is characterized by early metastases and cachexia.

Symptoms.—The general symptoms of cancer of the intestine are not different from those of cancer elsewhere. Loss in weight, anemia, cachexia, and depression due to toxemia are all demonstrable at some time in the course of the disease. Occasionally there is low intermittent or continuous fever. The onset of general symptoms varies considerably with relation to the character as well as the position of the growth. Should stenosis occur early, pain, constipation, or diarrhea, and the other symptoms common to partial or complete obstruction may first call attention to the disease. This also applies to hemorrhage or the development of an abdominal mass. The character of the growth (hard, or soft and ulcerating) also appears to determine the onset of cachexia and loss in weight. Sarcoma is characterized by early cachexia and loss in weight. It metastasizes early and seldom causes stricture. Very rarely a liposarcoma precipitates intussusception or volvulus before cachexia becomes evident.

In *cancer of the duodenum*, pain and irregular gastric symptoms are common in the early stages. When obstruction results from suprapapillary involvement it cannot be differentiated from pyloric obstruction. In circumpapillary cancer, jaundice, which increases and becomes profound, is the rule. The associated chills, fever, and jaundice may suggest a Charcot syndrome (impacted stone in common duct), but the history of repeated periodic attacks for a considerable length of time, which is usual in the latter condition, is lacking. The vomiting of bile and the passage of light colored stools are manifestations of infrapapillary involvement. A slightly

movable mass just to the right of the midepigastrium may occasionally be palpated in duodenal cancer.

Involvement of the jejunum or ileum may cause symptoms of obstruction. When the lesion is high, vomiting is more usual than when the growth is low in the small intestine. Meteorism is more general with the lower lesion. Constipation is the rule, but this often alternates with diarrhea and the passage of bloody mucus or blood. In not a few cases diarrhea is the initial symptom reported. The tumor mass is usually freely movable. As the obstruction is gradual in onset, visible peristalsis due to compensatory hypertrophy of the intestinal musculature is common. "Ladder pattern" distention suggests that the obstruction is low in the small intestine. The colicky pains of this obstruction are sharp and the waves of pain recur at shorter intervals than in colonic obstruction.

In *cancer of the upper colon* the symptoms are similar to those of growths in the small intestine. Constipation alone or alternating with diarrhea is a common early symptom. A localized sense of weight rather than pain may be the first manifestation noticed, but when obstruction begins, colicky pains occur and increase. Localized complicating peritonitis produces localized pain of an aching type. General distention is common. The "inverted horseshoe" type of distention is characteristic of low obstruction. The presence of a mass is of diagnostic value, particularly when it can be palpated in the lower left abdominal quadrant. This suggests involvement of the lower part of the descending colon or sigmoid. A mass in the transverse colon is usually freely movable.

Cancer of the appendix is rarely diagnosed except at operation. When a mass is present it cannot be differentiated from cancer of the cecum, which, if palpable, is found in the lower right quadrant and is only slightly movable.

The symptoms of partial obstruction of the colon not infrequently subside after a course of laxative medication, and relief may follow for some time, occasionally for months; sooner or later, however, they recur, and each recurrence is apt to be more severe in every way than the previous one.

Cancer of the rectum, which is one of the commonest of neoplasms, usually produces characteristic symptoms. If it is high, it cannot be differentiated from a growth in the sigmoid except by *x*-ray or the proctoscope. Those near the anus soon cause difficult and painful defecation, tenesmus, and frequent and painful micturition. The sudden development of hemorrhoids in a patient of cancerous age who has not previously suffered in this manner is suggestive, as is also the sudden onset of constipation in such an individual who has previously had regular bowel habits. Blood and mucus-coated pencil-shaped feces are also suggestive. Any of these symptoms in patients of the cancerous age demands digital and, when possible, proctoscopic and *x*-ray examination. Pus in the feces is always suggestive, also occult or visible blood.

The course of cancer of the intestines is variable as to length of time. In the small intestine, where it is usually rapid, particularly when in the duodenum, it lasts from a few weeks to a year. Cancer of the colon may be relatively chronic and occasionally persist for several years.

Diagnosis.—Growths of the intestinal tube which do not cause early obstruction or functional digestive disturbances are seldom diagnosed before it is too late for radical treatment to give any permanent relief. Functional

disturbances of digestion at all ages deserve careful consideration, but more especially in middle-aged and elderly individuals. Diarrhea of sudden onset in those of previously regular bowel habit should be explained, for this is the initial symptom of gastro-intestinal cancer in a considerable percentage of cases. Hemorrhoids and any evidence of blood or pus in the feces demand investigation. No physical examination is complete without digital exploration of the rectum. The chief aid in diagnosis is the *x*-ray. Careful *x*-ray studies of the gastro-intestinal tract rarely fail to establish diagnosis, even in the early stages. Films are more reliable than the fluoroscope for this, but administration of a barium enema on the fluoroscopic table is an essential part of the gastro-intestinal examination. *Tuberculous disease* of the intestine is difficult to differentiate from cancer. The *x*-ray shadow of these lesions is sometimes confusing.

Treatment.—The treatment of cancer of the intestine is essentially surgical. If it be instituted early in the disease a fair measure of success may be hoped for, particularly with neoplasms of the colon and rectum. For occlusions of the upper tract, lavage and rectal feedings have a place in palliative treatment. A concentrated diet is necessary with partial occlusion. The treatment of these growths by radium and deep high-voltage *x*-ray therapy has not proved, on the whole, of lasting benefit in any considerable percentage of cases. It is too early to predict the ultimate value of this method of treatment.

Benign Growths.—Non-cancerous growths of the intestines are relatively rare. They occur at all ages and about equally in both sexes. Among the commonest are adenomata, fibromata, myomata, leiomyomata, angiomata, and lipomata. They may be pedunculated, attached by a broad base, or merely a thickening or enlargement of the walls of the intestine, which projects into the lumen or from the outside of the tube into the peritoneal cavity. They are often multiple (polyposis). While these benign growths rarely cause symptoms, they are important in differential diagnosis. This is particularly true of the adenomatous polypi that form in the rectum and pelvic colon. When these ulcerate or bleed, as they are prone to do, it is difficult to differentiate them from cancers. Intussusception has been caused by a benign growth which pulled a section of the intestine into an invagination. Volvulus and kinks may likewise be produced by the weight of such a tumor. Occlusion of the intestinal lumen by the mass of a benign tumor is possible, though rare. The function of the rectum is easily disturbed by such involvement. It is not possible to state what percentage of apparently benign growths later become cancers through degeneration or local irritation of the adjacent parts. Adenomata and leiomyomata possess this potentiality far more than the other tumors mentioned.

Symptoms.—Aside from intermittent bleeding coupled with the chronic history of a mass, there are no symptoms characteristic of benign growths in the intestines. Pain is rare except when it is a protest against occlusion or pressure. When occlusion does occur it is usually of gradual onset and often recurrent. The symptoms are those of partial or complete obstruction, as the case may be. Diarrhea is fairly frequent in the partial occlusions. Bleeding from adenomatous polypi is rather common, particularly those low in the colon or rectum. Mucus is usually present in the stools. The character of these low growths can often be determined by proctoscopy or digital examination. Pedunculated tumors, which have become separated

by twisting of the pedicle, are occasionally passed. One can never be entirely sure if a palpable mass in the abdomen is cancerous or not. Time helps somewhat in the differentiation, although a cancer may develop very slowly. It is essential to consider age. While cancer, particularly sarcoma, is not entirely unknown in the young, benign growths are relatively common in young patients.

Treatment.—The treatment is nearly always surgical. Polypi that can be reached by the proctoscope should be snared off or otherwise treated topically. Hemorrhage may be relieved by the injection of various astringent solutions. Resection of considerable sections of the bowel has been necessary in some cases of extreme polyposis. The chances that an abdominal mass is non-cancerous are so slight that an exploratory operation should never be withheld on this account.

Arthur L. Holland.

AFFECTIONS OF THE MESENTERY

Mesenteritis.—General peritonitis involves the mesentery and the omental folds as well as the parietal and visceral coats. When localized in the mesentery the condition is called mesenteritis. Such localized inflammation is usually due to direct extension of disease from the adjacent intestine or the vessels (lymphatic or lacteal) which traverse the walls of the mesentery. Trauma or pressure may also cause mesenteritis. Chronic mesenteritis with fibrous thickening may seriously affect intestinal motility. The symptoms of mesenteritis are those of the underlying or primary diseases.

Structural Abnormalities of the Mesentery.—The structural abnormalities of the mesentery may cause serious dysfunction of the intestines and vessels which depend upon it for support. Abnormal length permits the formation of a volvulus or kinking with resulting acute intestinal occlusion or chronic recurrent partial obstruction. The local and general symptoms of vagatonia may in part at least be caused by the mechanical irritation to which the mesentery is subjected in splanchnoptosia. In slits or clefts and pouches (usually atavistic phenomena) loops of intestine may become strangulated or incarcerated (see chapter on Acute Intestinal Obstruction). Volvulus, intussusception, strangulation, and incarceration in their turn may seriously damage the mesentery. The acuteness and gravity of the symptoms in these accidents depend largely on the extent of such damage.

Mesenteric Hemorrhage.—The slight support which the mesentery affords its blood-vessels makes vascular rupture easy when the walls of the vessels are diseased. This occurs in aneurysm of the branches of the superior mesenteric artery and in arteriosclerosis, but is comparatively rare. Infiltration of blood between the mesenteric leaves from retroperitoneal sources is occasionally seen.

Mesenteric Vascular Occlusion.—Thrombosis and embolism with infarc-

tion are fairly common. The arteries may suffer embolism or thrombosis as the result of endocarditis, arteriosclerosis, or other vascular disease. Thrombosis of the superior mesenteric artery is always fatal. Venous thrombosis results from portal stasis, pressure on the venous trunks, suppurating disease of the intestine or appendix, and pylephlebitis. These vascular occlusions nearly always cause infarction. Gangrene, intestinal perforation, and general peritonitis are late results. Dynamic ileus is usual.

The *symptoms* vary somewhat with the cause, extent, and duration of the occlusion. Venous stasis may be responsible for indefinite abdominal distress which may pass unnoticed or be attributed to indigestion or an underlying disease such as cirrhosis or syphilis. This discomfort may be relieved from time to time, but with the formation of a thrombosis, signs and symptoms of serious acute abdominal disease suddenly develop. Acute, paroxysmal, abdominal pain, rarely localized, coincides with the onset, also reflex vomiting. In the early stages there is no increased muscular resistance and but little distention. This lack of increased resistance, with shock and severe abdominal pain which tends to subside after an hour or two, characterizes mesenteric vascular accidents. Acute constipation is the rule, but small, bloody, watery, or mucoid stools may be passed. With the onset of ileus come colicky pains, abdominal distention, and stercoraceous vomiting.

An accurate *diagnosis* is seldom made in these cases, although a history of arteriosclerosis is suggestive. The *treatment* is surgical. When operation is performed within a few hours of the onset a small percentage of patients recover.

Cysts and Growths of the Mesentery.—Blood cysts, echinococcus cysts, gas cysts, and dermoid cysts may involve the mesentery. Those peculiar to the mesentery are serous, lymphatic, or chylous in nature. They may be simple dilatations of the lymphatics or lacteals, or be of embryonic origin with fibrous or muscular walls. The latter form is the more common. Occasionally a cyst migrates from behind the peritoneum to a place between the mesenteric leaves. A psoas abscess has been known to do likewise. Lipomata which may become sarcomatous are occasionally found in the mesentery. The malignant tumors are those common to other parts of the peritoneum. Their incidence as primary growths is relatively rare. Neoplasms, however, are prone to metastasize in the mesentery. Malignant disease may spread to the mesentery by extension from the intestine, the walls of its vessels, or its lymph-nodes.

There are no *symptoms* characteristic of mesenteric cysts. They are rarely diagnosed before operation. Mobility of an abdominal mass that progressively enlarges and seems to be posterior to the intestinal coils on palpation and percussion is significant. Cysts can rarely be differentiated from neoplasms of the mesentery. Age is of some diagnostic importance, and also the general condition of the patient. The *treatment* of these cysts and growths is surgical.

Arthur L. Holland.

Diseases of the Liver

JAUNDICE

(*Icterus*)

Jaundice is a condition characterized by a yellowish staining of the skin, mucous membranes, and body fluids with bile-pigment. It is not a disease, but must be regarded as a symptom with varying etiology and significance. Jaundice is of three types: (1) obstructive (so-called hepatogenous); (2) non-obstructive or hematogenous; and (3) infectious (toxic or hemohepatogenous).

Obstructive Jaundice.—Etiology.—Obstructive jaundice, comprising about 85 per cent. of all cases, may be caused by any of the following conditions:

(*a*) Obstruction of the ducts from within by gall-stones, inspissated bile and mucus, or parasites.

(*b*) Obstruction due to changes in the walls of the ducts caused by inflammatory swelling (cholangitis), new growths of the ducts, stricture, and possibly spasm. (Spasm has been suggested as a probable cause of so-called emotional jaundice.)

(*c*) Obstruction of the ducts from without by pressure from new growths, cysts, gummata, enlarged glands and adhesions, and rarely by

(*d*) Kinking or torsion of the ducts, which is said to be the result of displacement of the liver, stomach, or right kidney.

Symptoms and Signs.—The symptoms and signs may conveniently be grouped according to the system involved.

(*a*) *Skin and Mucous Membranes.*—The conjunctivæ first show the *yellow pigmentation*, which soon appears in the skin of the entire body. Care must be taken not to mistake for jaundice the yellowish discoloration caused by patchy masses of fat in the conjunctivæ. Artificial light cannot be depended upon to reveal the presence of a slight icteric tinge. The color may vary from a pale yellow to a deep olive green. In "black jaundice" the color is a greenish black, and is said to be due to oxidation of the bilirubin to biliverdin.

Pruritus, or itching, is usually present, especially in chronic cases, but may be entirely absent even when jaundice is marked. Pre-icteric pruritus probably is not, as Riesman thought, suggestive of carcinoma. It has been shown, however, that definite amounts of bile-pigment may be found in the blood-plasma when there is no visible jaundice and bile is not present in the urine.

Eruptions on the skin are sometimes observed. They may be of petechial, purpuric, or nodular (xanthomata) character. The latter are rare, and most often affect the eyelids, hands, and feet.

(*b*) *Body Fluids and Excretions.*—The urine varies in color from light yellow to brownish green. It sometimes becomes icteric before discoloration of the skin is visible. Gmelin's nitric acid test distinguishes bile-pigments from blood-pigment, santonin, etc. Traces of albumin and bile-stained casts are often present when jaundice is persistent or severe. If obstruction of the bile-ducts is complete, little or no urobilin appears in the urine, but if it is only partial, this substance is present in normal or even increased quantities. Bile-salts are found with the bile-pigments, but

because of their greater diffusibility may disappear from the urine (dissociated jaundice).

Blood.—Before the bile-pigment reaches the urine, it must, of course, appear in the blood plasma. The early discoloration which this produces may be of diagnostic importance when the color of the skin and scleræ is doubtful. French observers have called attention to instances in which the bile-salts associated with bile-pigment in the blood, pass into the intestine, and leave the pigment behind (dissociated jaundice). Brulé states that under such conditions the usual minute particles of fat (hemoconia) appear in the plasma after meals, whereas when obstruction is complete this does not occur. Van den Bergh has proposed a test of the serum which is intended to differentiate obstructive jaundice from the other forms, but its value in this connection is still not fully determined.

In long standing and severe jaundice the clotting time of the blood is markedly prolonged, and operations are often complicated by obstinate hemorrhage. This is said to be caused by a reduction of the calcium content of the blood and may best be obviated by intravenous administration of calcium chlorid.

Jaundice, alone, does not increase the leukocyte count, but if prolonged may reduce the red cell count.

Cerebrospinal Fluid, Tears, Sweat, etc.—Tears, saliva, and milk are seldom stained, but the sweat is often markedly tinted. All tissues of the body except the central nervous system are discolored. The cerebrospinal fluid is usually unaffected.

(*c*) *Cardiovascular System.*—In early uncomplicated jaundice the heart rate is slow and may be irregular. The bradycardia, which is due to the action of bile-salts upon the cardio-inhibitory mechanism, may be counteracted by full doses of atropin.

(*d*) *Gastro-intestinal System.*—The most striking feature of the gastro-intestinal system is the change in the color of the stools. Their "clay-colored" appearance is produced by three factors: the absence of bile; the presence of undigested fat in quantities, which, according to Müller, may be increased from the normal 10 per cent. to 55 per cent. or more; and the presence of bubbles of gas which results from putrefaction caused by intestinal indigestion

Constipation often occurs, as well as anorexia, nausea, and flatulence. The liver is usually enlarged and the gall-bladder is sometimes distended. If the obstruction is due to a calculus in the common duct, however, the gall-bladder is usually small on account of previous inflammation (Courvoisier's law).

(*e*) *Nervous System.*—There is usually mental depression, headache, drowsiness, and languor. In severe cases or in late stages the nervous symptoms may be very severe, and consist of delirium, stupor, or coma (cholemia). Yellow vision, so-called xanthopsia, is sometimes complained of, and is due to pigmentation of the vitreous humor.

The diagnosis, prognosis, and treatment of the various forms of obstructive jaundice are described under the headings of the conditions responsible.

Non-obstructive Jaundice (*Hematogenous Jaundice, Hemolytic Jaundice, Chronic Splenomegalic Hemolytic Jaundice*). Non-obstructive jaundice is generally regarded as of splenic origin, and is described in the section on Diseases of the Spleen.

Toxic and Infectious Jaundice.—Jaundice of toxic or infectious origin is a symptom of some condition, such as phosphorus, chloroform, or arsphenamin poisoning, pneumonia, septicemia, Weil's disease, syphilis, and certain obscure intoxications. The more important of these will be considered separately.

Phosphorus Poisoning.—*Pathogenesis.*—Wells has shown that the hepatic cells are killed by phosphorus and that liberation of their autolytic ferments leads to extensive breaking down of the liver. As a result, leucin, tyrosin, cystin, and sarcolactic acid are present in the blood and urine.

Morbid Anatomy.—All the organs undergo fatty change, but the liver seems especially damaged. It becomes large, friable, and yellow. Occasional small hemorrhages are seen. Microscopically the hepatic cells show marked fatty infiltration and degeneration of the cytoplasm.

Symptoms.—Evidences of severe gastro-intestinal irritation usually appear soon after the poison is taken. Intense nausea, vomiting, burning epigastric pain, and profound collapse are the usual symptoms. Should the patient live two or three days, evidences of hepatic damage appear, such as enlargement and tenderness of the liver and spleen, jaundice, and vomiting of grumous material (hemorrhage from mucous surfaces). Later drowsiness, delirium, and coma supervene and death ensues in a day or two. In some patients the course is more subacute and recovery takes place.

Diagnosis.—A history of the ingestion of phosphorus, with suicidal intent or by accident, is important. Match heads or rat paste are sometimes used. The occurrence of severe gastric disturbances before the onset of jaundice is suggestive. Phosphorus poisoning differs from *acute yellow atrophy* in that the liver is enlarged and the odor of the vomitus is characteristic.

Prognosis.—The mortality is high when the hepatic involvement is marked, but many cases run a chronic or subacute course and end in recovery.

Treatment.—In the early stages gastric lavage with an oxidizing agent (peroxid of hydrogen, 1 to 3 per cent.) or old turpentine (3 c.c. in emulsion) is an important form of treatment.

Arsphenamin Poisoning.—Whether or not the jaundice which has been observed to follow the intensive administration of arsenicals in the treatment of syphilis is sometimes a manifestation of syphilis, and not the result of treatment, it is certain that a severe type of toxic jaundice, resembling a subacute form of acute yellow atrophy, has been caused directly by such medication. In this the liver is reduced in size. The *symptoms* vary from a mild grade to those of acute yellow atrophy with death. Strathy has called attention to the acuteness of the cardiohepatic angle as demonstrated by *x*-ray. Bailey and McKay suggest that mercury may be an etiological factor in some instances and that the disturbance may be of the nature of a "Herxheimer reaction" in the liver. The *treatment* of the condition is partly dietetic and partly medicinal. The diet should be very light and relatively rich in carbohydrates. Sodium thiosulphate ($\frac{3}{4}$ $1\frac{1}{2}$ grams) is given intravenously once a day for ten days to render the arsenic in the liver and other tissues insoluble, and thus retard its excretion and toxic action.

Icterus Neonatorum.—Jaundice of the newborn may conveniently be divided into two types: (*a*) The mild form, from which recovery is usual; and (*b*) the severe form, which usually proves fatal.

The *mild type* occurs in about one-third of all infants, and while most commonly seen in hospitals, is not infrequently encountered in private practice. The jaundice appears about the second or third day, and lasts a week or more. Both urine and stools contain bile-pigment. The condition is symptomless, the prognosis good, and treatment unnecessary.

A rare form of mild catarrhal or infectious jaundice is caused by acute duodenitis. This does not differ materially from the catarrhal disease of older children.

The *severe jaundice* of the newborn is of three types: (1) that due to definite obstruction, such as congenital absence of the bile-ducts; syphilis of the liver or of the bile-duct; and gall-stones. These conditions are dealt with elsewhere.

(2) That caused by thrombophlebitis, or suppurative phlebitis, in which the infection begins at the umbilicus and extends along the umbilical vein. This sometimes develops into general septicemia. The pathology of the disease is that of septicemia or pyemia, namely, cloudy swelling of the tissues, abscesses, and bronchopneumonia.

The jaundice appears about the fifth day, with remittent fever, rapid pulse and respiration, vomiting, diarrhea, and umbilical or gastro-intestinal hemorrhage; the infant, at first restless, becomes comatose and dies.

Treatment consists in the administration of enemata, and minute doses of calomel as an intestinal antiseptic. Antistreptococcic serum has been recommended, as the *Streptococcus hemolyticus* is usually the infecting organism.

(3) Familial jaundice of the newborn. This type of jaundice exists at the time of birth or appears soon afterward and usually affects successive infants. The child soon becomes drowsy and may die in convulsions. At *autopsy* the organs appear bile-stained, all tissues except the cortex of the brain being affected. Petechial hemorrhages occur in the viscera; the spleen and liver are enlarged. The *prognosis* is bad. Rolleston recommends administration of sodium salicylate and hexamethylamin to the mother as a *prophylactic measure*, and *treats* the infant with minute doses of calomel.

Acute Yellow Atrophy.—*Definition.*—Acute yellow atrophy is an acute diffuse necrosis of the liver cells as the result of intoxication or infection, and is characterized by a progressive diminution in the size of the organ, jaundice, and profound toxemia.

Etiology.—The condition is rare. Rolleston states that he has seen it only thirteen times in thirty-four years, except when it was due to definite agents, such as arsphenamin, trinitrotoluene, etc. The disease is said to develop more often since the introduction of these chemicals into common use. It occurs in individuals of all ages, but most frequently in the third decade of life. Women suffer from it more often than men, probably on account of pregnancy, the toxemia of which appears to be definitely related to that of acute yellow atrophy. Certain infections, such as syphilis, are sometimes held responsible. In cases associated with lues it is often difficult to determine whether the syphilitic infection or the arsphenamin treatment has brought on the condition. There are cases reported, however, in which the jaundice of the early stage of syphilis developed into acute yellow atrophy without administration of arsphenamin. Alcoholism has been followed in a few instances by acute yellow atrophy. Probably any

condition which leads to impairment of the resistance of the liver cells may be of etiological significance. Pre-existing disease of the liver is sometimes a factor.

Pathogenesis.—The resemblance of the condition of the liver in acute yellow atrophy to that in various forms of poisoning (phosphorus and chloroform) indicates that the probable cause of the changes is to be found in some form of toxemia which damages the liver cells and results in subsequent autolysis and destruction. It is thought that the jaundice is due to obstruction of the smaller bile-ducts by viscid secretion and desquamated cells. MacCallum suggests that it follows degeneration and consequent obliteration of the bile capillaries.

Morbid Anatomy.—The liver is greatly diminished in size, the weight often being reduced to one-half or one-third of normal. The surface appears shrunken and wrinkled. The atrophy may be more advanced in the left lobe. The color is yellowish green and in some areas dark red. On section, the liver is yellowish and contains scattered, depressed areas of reddish color. These are the more seriously degenerated portions. When atrophy is subacute raised areas of yellowish or greenish color may be seen which are due to compensatory regeneration. The marking of the lobules is indistinct, especially in the red areas. The liver tissue is soft and friable. The bile-ducts contain mucus only and the gall-bladder may be empty or contain a small amount of bile.

Microscopically, there is such wide-spread degeneration of the liver cells that it is difficult to recognize the organ. The lesions are more advanced in the reddish than in the yellow areas. The cells are in all stages of necrosis. They first become granular and bile-stained; then fragmentary degeneration takes place in the nuclei, which soon lose their staining power. In certain regions, particularly around the central veins, where the cells appear to undergo complete destruction, only the débris and the fibrous and vascular framework of the organ can be seen. The increase in fibrous tissue in such cases is only apparent. Hemorrhages occur here and there between the cells.

In the subacute cases the surviving liver cells at the periphery of the affected areas and the cells of the interlobular bile capillaries show evidence of compensatory regeneration (hyperplasia). This and the regeneration of the liver cells results in the formation of areas, or nodules, which stand out from the surrounding shrunken tissue. If the disease does not rapidly prove fatal, fibrotic changes may take place in the interstitial tissue (cirrhosis). Chemical investigation shows the presence of amino-acids, particularly leucin, tyrosin, and other substances, the products of autolysis and destruction of the cells of the liver. The quantity of fat is not increased, the yellow color being due to bile.

The other organs are stained with bile and often contain hemorrhages. The spleen is enlarged in about half of the cases. The epithelium of the kidneys undergoes granular degeneration and the myocardium is softened.

Symptoms.—At the *onset* the symptoms are those of benign catarrhal jaundice and may in no way indicate the seriousness of the condition. Most commonly this stage lasts for five or six days, but in some instances—notably in syphilitic cases—persists for as long as three weeks.

The *second stage* sets in abruptly with grave symptoms. Severe headache, restlessness, delirium, vomiting, convulsions, transient paralysis, and

dilatation of the pupils, which are among the prominent features, are indicative of marked toxemia and irritation of the nervous system. The jaundice becomes deeper. Hemorrhages may occur into the skin or from the mucous surfaces. Abortion may occur. The temperature usually remains low, but may rise suddenly just before death. The disease proves fatal a few days after the onset of the severe symptoms, usually after the development of coma and stertorous breathing.

The liver begins to diminish in size at the onset of the second stage. It becomes flabby, falls away from the anterior abdominal wall, and is replaced by coils of the intestine. Consequently it is extremely difficult to ascertain the exact size of the liver by percussion, because the hepatic area is tympanitic. Strathy and Gilchrist point out that the cardiohepatic angle, as seen by *x*-ray examination, becomes more acute as the atrophy progresses. The spleen is usually enlarged.

The urine, which is scanty, becomes markedly bile-stained and contains albumin and casts. The quantity of urea is diminished and the ammonia nitrogen content increased, probably by failure of the liver to convert ammonium compounds into urea, or as the result of acidosis and the fixation of ammonia by organic acids. Leucin and tyrosin crystals are usually present. The coagulation time of the blood is prolonged. There may be moderate leukocytosis.

Diagnosis.—The important diagnostic features of this disease are the jaundice, marked cerebral symptoms in the second stage, and the progressive diminution in the size of the liver. The latter point serves to distinguish acute yellow atrophy from such other forms of severe jaundice as *Weil's disease* and *phosphorus poisoning*. In severe *trinitrotoluol poisoning* the liver also atrophies, but the history of exposure determines diagnosis and is easily obtained.

The line of demarcation between the clinical picture of acute yellow atrophy of the liver and that of cases not so violent in nature is less distinct than has been supposed. The clinical and pathological records of any large hospital contain cases which seem to occupy a border-line position between acute yellow atrophy and benign catarrhal jaundice.

Prognosis.—The disease usually proves fatal after about two weeks. Occasionally the course is more subacute and the illness lasts several weeks. Recovery is known to take place, but is followed by appearance of signs of cirrhosis of the liver. The prognosis in pregnant women is invariably bad.

Treatment.—Rolleston suggests that as a prophylactic measure chloroform should never be given to jaundiced pregnant women, and that mercury should be used in treating the benign jaundice of early syphilis.

The treatment of acute yellow atrophy is entirely symptomatic. The toxemia is combated by subcutaneous or intravenous injection of large amounts of saline solution. Intestinal antisepsis and purgation are advised. Plenty of water with sugar should be given to combat the acidosis. Bismuth may be used to relieve vomiting. The diet should consist largely of milk.

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AFFECTIONS OF THE BLOOD-VESSELS OF THE LIVER

Hyperemia may be either active or passive.

Active Hyperemia or Congestion.—Active hyperemia is physiological during digestion. Pathologically it results from (1) over-eating, alcoholism, and other dietary indiscretions; (2) sedentary habits; (3) infections, such as typhoid fever, malaria, and yellow fever; (4) true non-suppurative hepatitis; and (5) constipation.

Morbid Anatomy.—Since it is only in the infective type that there is opportunity for postmortem study of the liver, little if any accurate knowledge of the pathology of this condition is available. The liver is said to be uniformly congested and swollen. The hepatic cells suffer little if any change.

Symptoms.—The symptoms are a sense of fulness in the right hypochondrium, headache, malaise, depression, and indefinite digestive disturbances, such as anorexia, flatulence, and constipation. Objectively the liver is tender and slightly enlarged. The scleræ are often muddy and the complexion sallow.

Treatment.—*Prophylaxis* consists in the avoidance of habits which predispose to the condition. The actual *treatment* of the condition should consist of rest in bed, marked reduction in the food intake, and free purgation with calomel and salts. Hot compresses, poultices, or mustard plasters over the liver give subjective relief. After a few days the diet may be increased, the patient allowed to get up, and to undertake moderate exercise gradually. The condition is not serious in itself and, under treatment, seldom lasts more than a few days.

Chronic Passive Congestion.—*Etiology.*—Chronic passive congestion is very common and usually results from back-pressure of blood from the right auricle in mitral stenosis or insufficiency, or in chronic myocardial disease. Rarely, it is due to obstruction of the flow of blood from the venæ cavæ into the right auricle by enlarged lymph-nodes, mediastinal tumors, or other intrathoracic abnormalities, such as pulmonary emphysema, fibroid lung, chronic pleurisy, and adherent pericardium.

Morbid Anatomy.—The liver is usually markedly enlarged and engorged with blood. In long-standing cases structural changes always take place. On section the cut surface is peculiarly variegated, the dark red central portion of the lobule being surrounded by a grayish or yellowish zone, which produces an appearance not unlike that of the cross-section of a nutmeg, hence the familiar term "*nutmeg liver.*" Microscopical examination reveals distention of the central veins, which are surrounded by shrunken, poorly staining cells (pressure atrophy) and small hemorrhagic areas. The cells in the outer zones of the lobules (the lighter area) are cloudy or fatty. Whether pressure atrophy completely accounts for the condition of the cells in the central zone of the lobule is not certain. Some pathologists emphasize the fact that the central cells are farthest from the food-supply and suffer first from starvation and lack of oxygen.

When passive congestion of the liver persists for years the content of connective tissue increases, particularly within the lobule (cardiac cirrhosis). It is doubtful whether this is a true cirrhosis, for it seems more probable that when the liver cells atrophy the normal stroma of the liver remains and appears to comprise a greater proportion of the tissue.

Symptoms.—The symptoms are mainly those of the associated cardiac or other underlying causes. Those directly referable to the liver are pain and tenderness and a feeling of fulness over the right hypochondrium. Vague digestive disorders are common, and there may be slight jaundice. Portal obstruction with ascites may occur before general cardiac dropsy develops. The liver is enlarged, tender, and firm. In a small proportion of cases, especially in those with tricuspid insufficiency, pulsation is felt.

Diagnosis is rarely difficult, but, if the causal lesion be overlooked, the large tender liver may be suspected of harboring an *abscess.* If the patient be studied with particular reference to the condition of the circulation, this affection, as well as those of *cirrhosis hepatis, new growth,* and *fatty* and *amyloid liver* may easily be ruled out.

Prognosis.—The prognosis is that of the causal condition.

Treatment.—In determining the type of treatment the underlying cause is paramount. Direct hepatic therapy is seldom necessary. Aspiration to relieve the congestion is dangerous. Calomel and other cathartics may be given to deplete the portal circulation.

Portal Thrombosis (*Pylethrombosis, Pylephlebitis Adhesiva*).—Etiology.—Portal thrombosis occurs most commonly in cirrhosis of the liver, and when malignant growths penetrate the portal vein. It is also encountered occasionally in syphilis of the liver and in association with infective processes in the vicinity, such as cholangitis, appendicitis, and peptic ulcer. It is said to be due in rare instances to primary portal endophlebitis.

Diagnosis.—The diagnosis is exceedingly difficult, and in most cases is not made. In a patient with hepatic cirrhosis or intra-abdominal malignancy the sudden onset of ascites with other evidence of engorgement of the portal branches (hematemesis, melena, splenomegaly) should suggest portal thrombosis. If thrombosis takes place gradually, diagnosis is impossible.

Treatment is unsatisfactory, particularly in the acute cases. It should be designed to relieve symptoms. In syphilitic cases appropriate therapy is said to be of use in the earlier types. The acute form usually proves rapidly fatal. Recovery depends upon the establishment of an efficient collateral circulation, with ultimate fibrosis of the portal vein (pylephlebitis adhesiva).

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THE CIRRHOSES OF THE LIVER

For practical purposes it is convenient to divide the cirrhoses of the liver into two main classes, portal and biliary. The term "cirrhosis," which was first applied by Laennec, refers to the tawny color of the surface of the liver in the commoner (portal) type, but it has since, by common usage, become synonymous with fibrosis. "Portal cirrhosis" includes, besides ordinary portal cirrhosis (the atrophic cirrhoses of Laennec), certain less common forms; namely, (1) the form associated with splenomegaly in Banti's disease; (2) portal cirrhosis with progressive lenticular degeneration (Wilson's disease); and (3) the cirrhosis of hemochromatosis. These are described elsewhere. Of the biliary type there are two varieties: Hanot's hypertrophic biliary cirrhosis and the obstructive biliary cirrhosis of Charcot.

Portal Cirrhosis (*Laennec's Cirrhosis, Atrophic Cirrhosis, Alcoholic Cirrhosis, Hob-nail Liver, Gin-drinker's Liver*).—Etiology.—Portal cirrhosis is, as a rule, a disease of middle age. It may, however, occasionally develop in young children. The condition usually appears in individuals about forty years of age and terminates fatally in the early fifties. Men are affected more often than women (2 to 1). Occupation and station in life seem to have no influence other than that of possibly exposing the individual to alcoholism.

In spite of attempts, especially in recent years, to explain portal cirrhosis on the basis of infection, or "subinfection" and intoxications other than with alcohol, very strong clinical opinion still points to *alcohol* as the chief etiological factor. This poison may act directly on the liver cells, after absorption into the portal system from the gastro-intestinal tract, or indirectly by injuring the gastro-intestinal mucosa, and producing a catarrhal condition which leads to chronic portal infection or intoxication. Whatever the mode of action, it is certain that the disease is very common in men who drink distilled liquors steadily and in excess.

Attempts have often been made to detect substances in alcoholic beverages, other than the alcohol itself, which might produce the hepatic lesions. Potassium sulphate and copper sulphate have been suggested as impurities of this nature, and there is some experimental evidence to support this view.

The ingestion of *highly seasoned foods* is also believed to be a contributing factor in some cases, particularly among the Mohommedans and Chinese, who do not use alcohol. *Infection* has been shown to be important, especially in syphilis, which may produce lesions quite similar to those of ordinary portal cirrhosis. Adami has described bodies in the liver which he considers to be disintegrating colon bacilli. He believes that these are carried from the intestine to the liver in the portal vein, that they exist for a while in the liver cells, finally die without multiplication (subinfection), and liberate endotoxins which stimulate the production of fibrous tissue. Experimentally, Opie found that bacteria injected into the blood after chloroform poisoning produced cirrhosis more readily than either of these agents alone. Experimental cirrhosis has also been produced by alcohol, by hemolytic sera, and by foreign proteins in sensitized animals.

Morbid Anatomy and Pathogenesis.—While the liver is usually smaller than normal, because of the contraction of the fibrous tissue and atrophy of liver cells, it is often enlarged, especially when there is much fatty change. This "fatty cirrhotic liver" is usually smooth and yellowish-white, not unlike that of the ordinary fatty liver, but its texture is firm and the tissue cuts with resistance on account of the increased quantity of connective tissue in the portal areas. In the ordinary type the surface is granular, with elevations or "hob-nails," the size of which varies from that of a pinhead to that of a pea or bean. It is greenish-yellow in color and surrounded by a greenish-white depression (contracted fibrous tissue). The elevated areas are islands of regenerated liver cells which are constantly present, or lobules or portions of lobules of original liver tissue. On section, the surface appears variegated, small areas of greenish-yellow or yellowish-brown being surrounded by grayish-white bands of fibrous tissue. The yellowish areas correspond to the elevations on the capsular surface, and therefore represent the normal or hyperplastic liver tissue.

Microscopically, the fibrotic changes are seen to involve the portal areas. In certain parts the fibrosis may be unilobular and enclose only a very small

area of liver tissue, but more often groups of lobules are enclosed together. The liver lobules themselves are distorted or atrophied, the central vein coming to occupy an eccentric position because the degenerative changes are more marked on one side of the lobule than the other. The hepatic cells may show changes of a hyaline nature in the early stages, and fatty changes are very prominent. Pigmentation of the cells with bile and hemosiderin may be noted. The latter is hematogenous in origin and may be associated with similar pigmentation in the skin and pancreas. This condition is most often associated with diabetes, to which the name *bronzed diabetes* is given. In certain areas evidence of regeneration of the parenchyma is to be seen in the shape of new cells of large size arranged in nodular masses near the periphery of the lobule where the blood-supply is most abundant. The portal areas also show evidences of proliferation of the cells of the bile-ducts (pseudobile canaliculi) and contain numerous well-formed blood-vessels derived from the hepatic artery.

The most conspicuous feature, however, whether on macroscopical or microscopical examination, is the tremendous increase in the fibrous tissue of Glisson's capsule on the liver surface and throughout its ramifications along the portal radicles. The obvious result is a marked obstruction of the portal circulation. Evidence of an attempt to overcome this by establishing an efficient collateral circulation is easily demonstrated: (1) The veins at the lower end of the esophagus anastomose with the coronary vein of the stomach, and form large varicose trunks; (2) the inferior mesenteric veins anastomose with the hemorrhoidal veins and often give rise to well-marked hemorrhoids of clinical importance; (3) anastomoses form between the epigastric and portal veins by way of the para-umbilical vein of Sappey. Consequently, there may form about the umbilicus a large group of varices radiating outward to join the epigastric veins (caput medusæ). Anastomoses also develop through the suspensory ligament between the portal veins of the liver and the veins of the diaphragm, emptying into the vena azygos; (4) through the veins of Retzius which connect the portal radicles in the intestines and mesentery to the inferior vena cava (retroperitoneal veins).

Changes in other areas are largely the result of the portal obstruction. Ascites is usually a marked feature, the spleen is enlarged by congestion and possibly as the result of toxemia, the gastric and intestinal mucosa are congested and catarrhal, and the pancreas often shows chronic interstitial fibrosis. General arteriosclerosis is common. Arteriosclerotic changes in the kidneys are noted in about 25 per cent. of the cases. Tuberculous peritonitis is occasionally found.

The sequence of events in portal cirrhosis is generally believed to be (*a*) degeneration of the liver cells in the periphery of the lobules caused by poisons carried in the portal vessels; (*b*) regenerative hyperplasia of the remaining liver cells and bile ducts with proliferation of the interstitial tissue, and contraction; (*c*) portal obstruction and the attempt to establish a collateral circulation. The increase in fibrous tissue may be partly due to replacement and partly to an inflammatory reaction to the causative toxin.

Symptoms.—It is by no means uncommon for portal cirrhosis to exist unsuspected during life and only be found after death from accident, intercurrent infection, or other disease. The early recognition of the disease,

therefore, may be extremely difficult, and often the first signs are those due to well-developed portal obstruction such as hematemesis or ascites. Careful investigation, however, usually reveals evidences of gastric disturbances, such as loss of appetite, nausea, flatulence, and occasional vomiting. These symptoms may appear periodically. Often such symptoms in an alcoholic subject are considered to be the result of alcoholism itself, as indeed they may be, and the onset of symptoms directly referable to the cirrhosis is frequently overlooked. Sooner or later, however, unmistakable signs usually appear. Osler conveniently divides the symptoms into two groups—obstructive and toxic.

Obstructive Symptoms.—The congestion of the gastric and intestinal mucosa produces nausea, loss of appetite, and even vomiting, especially in the morning. The bowel movements are irregular, the skin sallow, and the conjunctivæ muddy. The tongue is often coated and the breath offensive. As the obstruction progresses bleeding may take place from the esophageal varices, or from the bowel, and cause hematemesis and melena, the latter being usually due to blood which has passed from the stomach into the bowel. The hematemesis may be the first symptom, but usually occurs after obstruction of the portal flow has become quite marked. About 25 per cent. of patients vomit blood; of these, approximately one-fifth die from hemorrhage. There is usually rupture of the esophageal varix, but occasionally the hemorrhage is due to oozing from the gastric mucosa. In well-established cases secondary anemia may be marked and even fatal. Cirrhosis itself usually does not produce fever, but the patient has a poor resistance to such infections as tuberculosis or pneumonia, and may have a high temperature as a result of such intercurrent disease.

Ascites develops in about 50 per cent. of cases, and in the great majority of those who die of the disease is a prominent feature. It is said to be due not only to portal obstruction, but in certain cases to chronic peritonitis (tuberculous and otherwise), to toxemia, or to cardiac failure. The abdomen may be enormously distended and contain as much as 15 or 20 liters of fluid. The ascitic fluid is yellowish or straw colored, with a specific gravity below 1.016. It is usually clear, but may be somewhat turbid because of chronic peritonitis or previous tapping. The predominating cells are endothelial in type, but there may be numerous lymphocytes, especially if a tuberculous or syphilitic peritonitis be present.

Enlargement of the spleen may be due to the toxemia as well as to the venous congestion. This organ can usually be felt in spite of the abdominal distention. In the early stage the liver is enlarged and tender; the increase in size frequently persists until death.

The urine is decreased in amount, concentrated, and contains an excess of urobilinogen. Jaundice is usually absent, and when it does occur is not persistent.

Toxic Symptoms.—Although toxic symptoms usually develop during the later stages of the disease, they may appear at any time. If early, they are not likely to be severe—depression, headache, loss of memory, and general malaise being the most common. Later, or at any time, more marked signs of toxemia, such as delirium, drowsiness, coma, or even convulsions, may appear. The nature of the toxemia is unknown, but is believed by some to result from metabolic disturbances caused by loss of liver function.

Complications.—It is often difficult to distinguish sharply between what may be regarded as less common symptoms and complications. As has been mentioned before, tuberculosis of the peritoneum and lungs develops quite frequently, the latter, according to various authorities, being the cause of death in from 10 to 13 per cent. of cases. So-called "bronzed diabetes" may rarely be present. Thrombosis of the portal vein is also rare. The supervention of an acute infection, such as pneumonia, erysipelas, endocarditis, or peritonitis, is frequent.

Diagnosis.—During the early stages of portal cirrhosis the symptoms are so vague that definite diagnosis is often very difficult. In an alcoholic patient, or an individual who has led an irregular life, persistent dyspepsia with repeated attacks of "biliousness" and perhaps slight jaundice should arouse suspicion of early hepatic cirrhosis. Added confirmation is given if the liver be enlarged and tender and the spleen enlarged. Later the "hepatic facies" is characteristic; the patient is thin, the eyes sunken, the nose sharp, distended venules appear on the nose and cheeks, and the skin is muddy or subicteroid. Definite signs of portal obstruction render the diagnosis certain.

The ordinary portal cirrhosis can be differentiated from the *syphilitic type* by the absence of a history of infection and a negative reaction to the Wassermann test. It must be kept in mind, however, that syphilis may and often does exist in a patient with non-syphilitic portal cirrhosis. Hematemesis without ascites may suggest *peptic ulcer*. In this condition pain has a definite relationship to the taking of food, and the liver and spleen are not enlarged. Fluoroscopic examination after a barium meal helps to exclude the possibility of ulcer and *malignant disease* of the gastro-intestinal tract. The spleen is usually enlarged in malignant disease of the liver, and its outline can often be felt to be nodular and umbilicated; this condition does not develop in cirrhosis. Jaundice is more frequent, deeper, and more persistent in carcinoma. *Hanot's cirrhosis* is characterized by intense and persistent jaundice, a more chronic course, the absence of signs of portal obstruction, and its appearance in young individuals. In *Banti's disease*, which often occurs in young subjects also, the splenic enlargement is primary and may be enormous; secondary anemia is marked.

Prognosis.—Accurate prognosis is impossible on account of the wide variations in the course of the disease. At times when there are no major symptoms, the disease may remain unrecognized throughout life and the victim die from some other cause. Again the disease may be acute and end fatally in a few months. The great bulk of cases fall between these extremes, and the average duration from the onset of definite evidence of cirrhosis until death is about two years.

The development of a collateral circulation may be so adequate as virtually to relieve the portal obstruction. Hyperplasia of the liver cells may be sufficient to obviate the toxemia, and allow the disease to become latent, so that, to all intents and purposes, the patient is cured.

Death is usually due to toxemia, inanition, or intercurrent infection. Sometimes hemorrhage from the esophageal varix may prove fatal.

Treatment.—In the pre-ascitic stage, and before hematemesis has occurred, the therapeutic measures should rectify the patient's mode of life and personal hygiene. Alcohol should be prohibited, large quantities of water taken, and the bowels well regulated with saline. The diet should be

simple, and free from highly seasoned foods. Milk, if well tolerated, should be used freely, but eggs, meats, and fats should be restricted. Suitable exercise and appropriate hydrotherapy are necessary. Spa treatment has been recommended, and is especially serviceable in establishing new and wholesome habits of diet and hygiene.

If syphilis is coexistent, its specific treatment should be employed. Special emphasis must be placed upon the thorough use of potassium or sodium iodid, a drug which is said to exert a beneficial effect even in non-syphilitic cases.

For *hematemesis* the patient should be kept absolutely quiet in bed, and all food be omitted for two or three days. An ice-bag should be placed over the epigastrium, and, if the patient is restless, morphin given hypodermically. When the hemorrhage is severe, normal horse-serum (10 c.c.) may be injected intramuscularly to increase the coagulability of the blood. Human blood may also be similarly administered. After the hemorrhage has ceased, and if ascites is absent, normal saline or 10 per cent. glucose in saline may be given by the Murphy drip or interstitially to dehydrated patients.

At the onset of ascites, purging with salines, restriction of the fluid intake, and the use of such diuretics as theocin, theobromin, caffein, or digitalis may be sufficient to inhibit its development. Eventually, however, tapping is necessary. It is not uncommon for the fluid to cease to accumulate after repeated tapping, presumably because of the establishment of venous anastomoses at the site of the puncture wounds. The abdomen should be tapped promptly whenever the amount of fluid causes embarrassment to respiration or cardiac action, or even discomfort to the patient.

Surgical Treatment.—Omentopexy (Talma operation) has been more or less successful in certain cases in encouraging an anastomotic circulation. The mortality from the operation is 33 per cent., and in recent years this operation has seemed to lose favor.

Biliary Cirrhosis.—Two forms of biliary cirrhosis are recognized: the primary (Hanot), and the secondary or obstructive (Charcot).

Primary Biliary Cirrhosis (*Hypertrophic Biliary Cirrhosis, Hanot's Cirrhosis*).—*Definition.*—Primary biliary cirrhosis is a chronic disease of the liver characterized clinically by persistent jaundice with enlargement of the spleen and liver, and anatomically by a catarrhal inflammation of the small bile-ducts and intralobular fibrosis.

Etiology and Pathogenesis.—It is a rare disease which occurs in youth and early adult life. Males are more often affected than females. Although the disease is said to be familial or even hereditary in certain cases, a definite distinction has not always been clearly made between Hanot's cirrhosis and hemolytic (familial) jaundice. The immediate cause is unknown. Primary biliary cirrhosis has, in a number of instances, definitely followed an infection, such as typhoid fever. This fact and the clinical picture have led most observers to regard infection as the most probable cause of Hanot's cirrhosis. The usual absence of evidence of infection in the duodenum and larger bile-ducts renders the possibility of an ascending infection unlikely; and Rolleston inclines to the view that the infection (or toxin) reaches the small bile-ducts through the hepatic artery. The fibrotic changes are believed to be secondary to the cholangitis.

Morbid Anatomy.—The liver is uniformly enlarged, sometimes weighing 3800 gm. The surface is smooth or finely granular, dark green in color,

and may show some perihepatic adhesions. The organ is firm in consistency, cuts with resistance, and presents a uniform, granite-like, yellowish-green appearance. Microscopically a dense fibrosis can be seen to surround the individual lobules and small bile-ducts. It may actually extend into the lobule (intralobular fibrosis). The liver cells themselves do not undergo any marked change, and the larger bile-ducts are likewise comparatively unaffected.

In the portal areas the smaller bile-ducts show evidence of catarrh and proliferation, and in many cases contain dark-staining columns of cells, the so-called *pseudobile canaliculi*. These structures are formed in an attempt at regeneration, a reactive hyperplasia of the cells of the bile-ducts.

When the disease is advanced the picture may be confused by the development of a multilobular cirrhosis. Indeed, it is often very difficult to classify certain borderline cases from a histological standpoint.

The spleen is enlarged and shows endothelial proliferation and fibrosis. The periportal lymph-nodes are enlarged and often all the glands. All the organs are stained with bile.

Symptoms.—The *onset*, which is insidious, is sometimes manifested by vague gastro-intestinal symptoms, such as mild dyspepsia, pain, vomiting, and diarrhea. Often the first definite symptom is jaundice, but this may be preceded by pruritus. The jaundice is usually slight but persistent; it may vary in degree from time to time. The urine and feces contain bile. The liver is found to be enlarged and may be tender. The spleen is palpable. Periodic attacks of mild fever, abdominal pain, leukocytosis, and progressive hepatic and splenic enlargement and tenderness may occur. There is no evidence of portal obstruction unless multilobular fibrosis supervenes in the advanced stage.

The *course of the disease* is chronic, the symptoms gradually becoming more pronounced, and the general nutrition of the patient failing as time elapses. Three to six years is a common duration. Death results from an acute degeneration of the liver cells resembling acute yellow atrophy, or from profound cachexia. In the later stages hemorrhages into the skin and from the mucous membranes may occur. Clubbed fingers have been noted.

Diagnosis.—The insidious onset in young persons of a mild but persistent jaundice, gastro-intestinal disturbance, enlargement of liver and spleen, and periods of slight fever, leukocytosis and abdominal pain, should suggest hypertrophic biliary cirrhosis. The condition must be differentiated from *portal cirrhosis* (age, signs of portal obstruction, history of alcoholism), from *cholelithiasis or other types of obstructive jaundice* (history, deep jaundice, clay-colored stools, slight enlargement of liver and spleen), and from *hemolytic jaundice* (acholic urine, increased fragility of red cells).

Treatment.—The disease cannot be definitely arrested. The general health should be maintained in so far as possible by careful avoidance of exposure to cold and wet, a generous but simple diet, and plenty of sunlight and fresh air. The pruritus may be relieved by measures already recommended for that of other types of jaundice. Administration of calomel (gr. $\frac{1}{8}$, three times a day for several days) has been recommended. Drainage of the gall-bladder and bile-ducts gives good results in certain cases, but has not come to be a routine method of treatment. Lyon's method of non-surgical drainage of the gall-bladder and bile-ducts by the duodenal tube

may produce equally good results without incurring danger. W. J. Mayo has reported that splenectomy was a successful form of treatment in 3 cases.

Obstructive Biliary Cirrhosis (*Secondary Biliary Cirrhosis, Charcot's Cirrhosis*).—Obstructive biliary cirrhosis results from the proliferative fibrosis brought on by chronic obstruction of the larger bile-ducts by gall-stones, new growths, or adhesions. As the name implies, the fibrosis extends out from the intrahepatic bile-ducts and produces a condition not unlike that of Hanot's cirrhosis, except for the less marked enlargement of the liver. A cholangitis involving the larger bile-ducts is also present. The gall-bladder may or may not be distended, according to the nature of the obstruction (see Courvoisier's Law).

Symptoms.—The symptoms are those of the cause of the obstruction and those of chronic obstructive jaundice. The liver is definitely enlarged and firm. Recurring attacks of chills and fever (Charcot's intermittent hepatic fever) are common. The spleen is not uniformly palpable as in Hanot's disease.

Treatment.—The treatment is that of the cause of the obstruction, and is usually surgical.

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ABSCESS OF THE LIVER

(*Suppurative Hepatitis, Purulent Hepatitis*)

Etiology.—Suppurative hepatitis or abscess of the liver is always due to infection. The organism may be carried to the liver by either the portal or hepatic blood-stream; by the bile passages after suppurative cholangitis; by direct extension from neighboring infection; and from external sources by traumatism.

The commonest type is that in which multiple abscesses develop as a result of infection by emboli from foci in the area drained by the portal vein, or as a manifestation of a general pyemia, in which the infective agent reaches the liver through the hepatic artery. Rarely the infection has been known to be carried in the hepatic veins (retrograde emboli). In the portal area the emboli arise from ulcerative disease of the gastro-intestinal tract, from acute appendicitis, rectal and pelvic infections, and following rectal or low abdominal operations for herniæ, hemorrhoids, etc. In such cases, as Osler points out, the abscesses are, as a rule, within the branches of the portal vein (suppurative pylephlebitis). If infection takes place by way of the hepatic artery it is secondary to such conditions as ulcerative endocarditis, septicemia, and pyemia.

Tropical abscess (*solitary* abscess) is usually single and is caused almost always by infection with the *Entameba histolytica*. As its name implies, the disease occurs most commonly in tropical climates. It is ordinarily the result of previous amebic dysentery, but may develop without infection of the bowel. Overindulgence in alcohol and overeating are said to be predisposing factors. The incidence is higher among the foreign population in India than among the natives. The route by which the organism reaches the liver is not definitely known, but the general weight of opinion is that it travels by way of the portal vein. Amebic abscesses may form many years after an attack of dysentery.

Suppurative cholangitis is not an uncommon precursor of hepatic abscess. The infection spreads by extension along the bile-ducts into the liver substance. Direct extension may also occur from an infected gall-bladder, from a subphrenic abscess, or other suppurative lesion in the vicinity of the liver.

Traumatism is not a frequent cause of abscess of the liver. It may occur as a result of accidental injury or of a stab-wound in which the bacteria are introduced directly from without. The causative wound need not be perforating, as injury to the liver from indirect contusion or laceration may cause the localization of blood-borne organisms which come from infections elsewhere in the body.

The ordinary pyogenic organisms, such as *Streptococcus*, *Staphylococcus*, *Pneumococcus*, *Bacillus coli*, are those usually present in the abscess. Occasionally *Bacillus typhosus* or *Bacillus dysenteriæ* may be found. The *Tubercle bacillus* and the ray fungus (actinomyces) are rarely encountered.

Hydatid cysts in the liver may become infected with pyogenic bacteria and cause an abscess. Rarely the presence of round worms and flukes in the liver causes a purulent hepatitis.

Morbid Anatomy.—The tropical or amebic abscess is usually single and, in about 75 per cent. of cases, situated in the right lobe. The abscess may be very large and contain a surprising amount of material. As much as 8 quarts of fluid have been taken from a single abscess. Externally there may be perihepatic adhesions especially to the diaphragm. The abscess cavity is lined at first with rough necrotic tissue, but later the walls become smoother as fibrous tissue surrounds the abscess and invades the neighboring parts of the liver. The contents of the abscess are usually reddish brown in color, glairy in consistency, and under the microscope can be seen to contain broken-down liver and blood-cells and *Entamebæ histolyticæ*. Leukocytic infiltration of the wall is not the rule. An amebic abscess is, therefore,

really an area in which necrosis and digestion of the tissue have occurred, rather than a true abscess. In a certain number which become secondarily infected with pyogenic organisms creamy pus is present. Sometimes the amebæ can be found in the wall of the abscess when examination of the contents fails to reveal them.

Solitary abscesses of the liver are also occasionally caused by bacterial infection, particularly in cases of traumatism.

Pyemic abscesses and those secondary to suppurative cholangitis are usually multiple. The former type may be miliary, and are distributed along the course of the blood-vessels, while the latter extend into the liver substance from foci in the bile-ducts. Frequently multiple abscesses coalesce, so that the whole area involved assumes a spongy appearance because of the uneven areas, necrosis, and liquefaction.

The contents of the non-amebic abscesses are definitely purulent, and contain many pus cells, as well as detritus from broken-down tissue.

In suppurative pylephlebitis the infection originates in the area drained by the portal vein (appendiceal abscess, ischiorectal abscess) and sets up first a portal periphlebitis. The inflammation extends inward, involving the intima, and resulting in thrombosis. The thrombus becomes infected, softens, and in breaking down forms pus. The process may be extended to the liver by direct continuity, or by infected emboli from the suppurating area. The liver is uniformly enlarged and its entire portal area may be involved in the suppuration. The abscesses may be separate and produce a honeycombed appearance or may coalesce.

Symptoms.—Solitary Abscess.—Frequently a solitary hepatic abscess produces no special symptoms and may be unsuspected during life (latent abscess). Usually, however, a fairly definite syndrome permits correct diagnosis. In amebic infections the symptoms may develop during or after an acute attack of dysentery. The onset may be sudden, but is often insidious. Malaise, intermittent fever, chills, pain in the right upper quadrant with enlargement and tenderness of the liver, leukocytosis (except in amebic infection), and slight jaundice are commonly present. The chills and intermittent fever often suggest malaria. Profuse sweating is common. The pain is variable, often radiates to the right shoulder or scapular region, and if the abscess approaches the surface, may be sharp and stabbing in character. It is aggravated by deep breathing and palpation. With perihepatitis a friction sound may be heard over the liver. As a rule the patient is most comfortable when lying on the right side or back; turning to the left side often produces a dull aching or dragging sensation in the right hypochondrium. Loss of appetite, weakness, emaciation, and a "septic" appearance are usually present and progressive.

When the abscess is deeply situated the enlargement of the liver may be slight at first, and there may be no change in the contour of the organ. Later, when the abscess has attained a large size or when it is situated anteriorly and toward the lower margin, the enlargement is easily demonstrable, and a bulging of the right side of the abdomen may be detected. If the abscess is close to the diaphragmatic surface of the right lobe, an upward displacement of the right lung is evident on percussion and can be seen in *x*-ray plates. Abdominal breathing is restricted.

Jaundice develops in only 15 per cent. of patients and is not marked. A pale, muddy, or sallow appearance of the skin with subicteric tinting of

the sclera is, however, usual. Nausea and vomiting may occur and intestinal irregularities (diarrhea, constipation) are common.

Ascites is rare, and the spleen is seldom enlarged.

Pyemic Abscess and Suppurative Pylephlebitis.—The symptoms of pyemic abscess and suppurative pylephlebitis are masked to a large extent by those of the primary disease. The clinical picture is that of general septicemia or localized septic infection, such as appendiceal abscess, pyonephrosis, lung abscess, or other infection likely to give rise to pyemia. Chills, sweats, remittent fever, with malaise, vomiting, weakness, wasting, slight icteroid tinging of the skin and conjunctivæ, and tenderness over the liver are suggestive. There are, however, no signs pathognomonic of involvement of the liver, and usually the multiple abscesses are but one manifestation of the original infection. There is usually a pronounced leukocytosis (polymorphonuclear) in this type of hepatic abscess.

Complications.—The abscess may rupture if not operated on. This occurs not infrequently, and the rupture takes place most often through the diaphragm and pleural sac into the lung. A lung abscess is thus produced which may, in turn, rupture into a bronchus. If the infection be amebic, the sputum is then brownish (anchovy colored) and contains shreds of liver tissue and amebæ. Rupture may also occur into the bowel, into the peritoneal sac, and rarely into the pericardium. Secondary abscesses in the lungs are not uncommon.

Diagnosis of abscess of the liver is often difficult. A history of dysentery, the development of a clinical picture of sepsis (chills, sweats, irregular fever), and signs of hepatic involvement (enlargement, tenderness, pain in hepatic region) constitute the most significant signs in the amebic cases. *x*-Ray examination may be valuable. In pyemic abscesses the clinical picture is that of pyemia or septicemia, and often there is little evidence of involvement of the liver, although enlargement, pain, and tenderness over the liver may suggest the correct diagnosis.

In malarial regions the condition must be differentiated from *malaria*. Examination of the blood for the malarial parasite, the leukocyte count, and the therapeutic test with quinin suffice for this. Liver abscess may be distinguished from *suppurative cholangitis* by the occurrence in the latter of earlier and more pronounced jaundice and a frequent history of cholelithiasis. In "intermittent hepatic fever," associated with *gall-stones*, the differential features are the paroxysms of pain, chills, sweats, followed by deepening jaundice, with afebrile and (usually) apparently normal intervals. If the hepatic abscess is large and located in the upper part of the liver, the diaphragm may be high and the lung compressed. Such a condition may suggest *empyema*, but the history, the limits of dulness on percussion, and the *x*-ray findings usually suffice for differentiation. Diagnostic puncture of the liver may be employed if the presence of a solitary abscess is suspected, but involves some risk of hemorrhage and peritonitis. Blood examinations (cultures, counts, parasites, Wassermann test) should prevent confusion with *syphilis of the liver*, *trypanosomiasis*, *typhoid fever*, *leukemia*, and *malignant endocarditis*. The history, complement-fixation test, and exploratory puncture sometimes permit diagnosis of a suppurating *echinococcus cyst* in the liver.

Prognosis.—Multiple abscesses of the liver are practically always fatal, whether they be due to suppurative pylephlebitis, pyemia, or extension

from suppurative cholangitis. Solitary abscesses, on the other hand, may not prove fatal when rupture takes place into the bowel, or even into the lung, or when surgical evacuation is successful. If the abscess remains intact, death usually results from toxemia or pyemia.

Treatment.—The treatment of *solitary abscesses* is surgical. Evacuation and drainage of the abscess should be performed as soon as the diagnosis is made. If the infection is amebic, emetin should be given as well. Repeated aspiration of single abscesses has been recommended by some observers, as preferable to open drainage.

General therapy consists of absolute rest in bed, light diet, application of poultices or compresses to the hepatic region, and regulation of the bowels. During convalescence open air, nourishing food, and tonics are advisable.

The treatment of *pyemic abscesses* and *suppurative pylephlebitis* is purely symptomatic and palliative, since these conditions are almost invariably fatal.

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MALIGNANT DISEASE OF THE LIVER

Under the heading of malignant disease of the liver, carcinoma and sarcoma of the liver, both primary and secondary, will be considered.

Incidence and Etiology.—*Primary carcinoma* of the liver is rare, but is seen more often than primary sarcoma of the liver. It is more common in males than females, and occurs in individuals about fifty years of age. *Secondary carcinoma* of the liver is very common, and develops in about 50 per cent. of all the victims of malignant disease. The primary growth responsible for the secondary metastases in the liver is most commonly found in the stomach, but frequently occurs in other parts of the digestive tract, especially in the colon. Not infrequently the primary lesion is in the breast, the pancreas, the gall-bladder or the genito-urinary tract (prostate, uterus, etc.). Females are slightly more susceptible than males (4 to 3), probably on account of the frequency of cancer of the uterus. The patients are usually over forty years of age.

Primary sarcoma of the liver is extremely rare. *Secondary sarcoma* constitutes nearly 10 per cent. of malignant disease of the liver and is most frequently due to metastases from primary growths in bones, adrenals,

mediastinum, the eye, and the skin. The age incidence is that of sarcoma in general, and is therefore lower than that of carcinoma.

Morbid Anatomy.—Eggel divides primary carcinoma of the liver into three types: (1) The nodular and common form in which there are scattered tumors throughout the organ; (2) the massive form, in which a single large neoplasm is found, often with small metastatic nodules in its vicinity; (3) and the diffuse form, in which the whole liver is infiltrated with small cancerous nodules, surrounded with marked connective tissue hyperplasia. This latter type gives rise to a gross picture very like that of cirrhosis of the liver, which can often be recognized as malignant only on microscopical examination. Rolleston believes that the cirrhosis is primary and that the carcinoma is the outcome of hyperplasia of the hepatic cells.

Secondary carcinoma appears as multiple, grayish-white nodules of varying size and number, which, when superficial, often cause the surface of the liver to bulge and form definite bosses which may be umbilicated. Frequently these bosses are palpable through a thin abdominal wall. The liver as a whole may be enormously enlarged. Christian reports that in one case it weighed 33½ pounds. The nodules on section often show central areas of degeneration and hemorrhage so that the original firm consistency is lost. The shrinkage of the necrotic center and the contraction of the fibrous tissue produce the umbilication mentioned above. Microscopically the tumor presents the characteristics of the primary lesion, and is most commonly alveolar or columnar in structure.

Primary sarcoma of the liver is usually a massive growth. The tumor is often very hemorrhagic and may break down in the center to form pseudocysts. In another form there are multiple nodules, and occasionally a third type is seen which shows diffuse infiltration resembling that in the liver in congenital syphilis. Secondary sarcoma may be of the melanotic type, the primary lesion being in the eye or less commonly in the skin. Less important types are lymphosarcoma and myxosarcoma.

Symptoms.—The onset is very insidious and is manifested by weakness, loss of appetite, and failure in general health. As in the case of malignant disease elsewhere, there is usually progressive loss of weight and increasing secondary anemia.

Symptoms indicative of involvement of the liver itself may arise at any time. These are usually discomfort or pain in the right hypochondrium, jaundice, and ascites. It is often impossible to distinguish primary malignant disease of the liver from the secondary type, unless there is evidence of a primary growth elsewhere.

The enlargement of the liver is usually progressive. Often the irregular bulging of the right hypochondrium can be seen through a thin abdominal wall, and, on palpation, the bosses with their umbilicated centers may be felt. In such cases the diagnosis is certain. In other patients, however, the liver is not enlarged, and definite diagnosis is impossible. Jaundice which is apparent in about 50 per cent. of cases is usually due to pressure of a cancerous nodule upon the intrahepatic bile-ducts, but may be caused by the pressure of enlarged glands on the larger ducts. Ascites is common, but is not seen as frequently as jaundice. It may be due to pressure upon the portal vein by tumor nodules, to an associated hepatic cirrhosis, to perihepatitis, or to extension of the growth to the peritoneum. The spleen is usually not enlarged.

Irregular fever is a common symptom which may be caused by the cancer itself or by suppuration in a degenerating cancerous nodule. The blood examination reveals a secondary anemia and frequently a moderate leukocytosis. The urine contains bile pigment when the jaundice is deep. A positive Wassermann reaction in the blood, without other evidence of syphilis, has been reported. In one such case in Detweiler's experience the reaction was persistent, but antisyphilitic treatment had no effect on the progress of the disease. It is probable that the latent syphilis had no relation to the neoplasm.

Diagnosis.—An insidious onset with progressive nodular enlargement of the liver, anemia, and loss of weight and strength in a person at or past middle age, are characteristic signs. The diagnosis is conclusive if a primary malignant growth elsewhere be demonstrable. The presence of jaundice and ascites is additional evidence.

It is often impossible, in the absence of signs of a primary lesion, to distinguish between primary and secondary malignancy of the liver. The primary focus may be latent.

Syphilis of the liver may be recognized by the history of infection, the evidence of luetic lesions elsewhere in the body, the blood examination, and the therapeutic test. As pointed out above, the possibility of the coexistence of both diseases must be kept in mind. An *echinococcus cyst of the liver* may simulate cancer, but the history, the softer consistency of the tumor, the presence of hydatid thrill, and the slower development without marked cachexia are differential points. *Hepatic abscess* presents signs more characteristic of infection, namely, rigors and fever, marked leukocytosis and sweats. A history of amebiasis or a pyemic condition is common; jaundice or ascites, on the other hand, are evidences of cancer. *Portal cirrhosis* in its earlier stages may cause enlargement of the liver, but the enlargement is more uniform on palpation, there are evidences of portal obstruction, with enlargement of the spleen, the disease progresses slowly, and the liver tends to decrease in size. *Biliary cirrhosis* occurs in younger individuals; the enlarged liver is smooth, the spleen is enlarged, the jaundice early, and the course very chronic. *Obstruction of the common bile-duct with gall-stone* causes changes resembling those of malignancy, such as jaundice, and enlargement of the liver, with local pain and tenderness. The enlargement, however, is usually slight, while the pain is paroxysmal and associated with chills and fever. The jaundice tends to fluctuate and there is usually an antecedent history pointing to cholecystitis.

Prognosis.—As a rule, malignant disease of the liver terminates fatally within from three to twelve months after enlargement of the liver has been noted. The course of the primary is usually more rapid than that of the secondary type.

Treatment is chiefly palliative. Relief of pain is secured only by the use of morphin. This should be given in doses sufficient to keep the patient comfortable. If the liver is very large, a binder or supporting belt may be advantageously employed. The appetite is improved to some extent by the ingestion of dilute hydrochloric acid (1 dram with meals), and vomiting may be combated by the administration of bismuth, dilute hydrocyanic acid, or morphin. The bowels should be regulated by salines. For the itching, calcium lactate (gr. xv t. i. d.) may be given internally, and carbolic acid (1 : 60), or soda bicarbonate solution, externally. The hypo-

dermic administration of atropin, pilocarpin, or morphin is sometimes helpful in obstinate cases. Operation for removal of the tumor is rarely possible, but when the growth is solitary, such treatment may be justifiable.

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BENIGN TUMORS OF THE LIVER

Benign tumors of the liver are uncommon and are of little clinical importance. *Hemangiomata*, which are occasionally seen, are, as a rule, small and situated just beneath the capsule. Rarely, they enlarge during adult life and produce clinical signs such as bulging of the abdomen, ascites, or other symptoms of pressure. Solitary and multiple *adenomata* may occur. The latter type, which is found in some cases of portal cirrhosis, is regarded by some as merely an excessive hyperplasia of the liver tissue. It is difficult to draw the line between hyperplastic areas and adenomata, and between adenomata and carcinomatous nodules. Some pathologists consider the adenoma a transitional stage between hyperplasia and malignancy.

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CYSTS OF THE LIVER

Simple cysts are usually small and single. They are commonly attributed to local obstruction of the bile-ducts, either congenital or associated with inflammatory change. They have no clinical significance.

Cystic disease of the liver is a rare condition, usually associated with congenital cystic kidneys. The cysts are usually small, multiple, and filled with a clear serous fluid. The condition is probably congenital, although it is seldom recognized until adult life, and then only if the kidneys are affected.

Echinococcus cysts are discussed elsewhere.

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DEGENERATIVE DISEASES OF THE LIVER

Fatty Liver.—It has been the custom to consider fatty lesions of the liver as of two types—infiltrative and degenerative. The former type has been thought to be a condition in which fat derived from the usual fat deposits in other parts of the body is deposited in the liver, after transportation by way of the blood-stream, without any actual damage to the liver cells; whereas the latter type has been thought to be a primary degeneration of the protoplasm of the liver cells into fat. This distinction is not as sharp as such classification would imply since in certain conditions, such as phosphorus poisoning, in which the lesion is usually regarded as degenerative, some of the fat in the liver is derived from other parts of the body. Clinically, however, the degenerative types form a rather definite group, including phosphorus, arsenic, alcohol and chloroform poisoning, acute yellow atrophy, and occasionally acute infections. The infiltrative type is commonly found in (*a*) obesity; (*b*) conditions supposed to reduce the oxidative powers of the body, such as anemia, cachexia, and pulmonary tuberculosis; and (*c*) infections, such as septicemia, typhoid fever, and the acute exanthemata.

Morbid Anatomy.—The fatty liver is usually uniformly enlarged, smooth, with rounded edges, and pale. It is greasy on section and, as a rule, appears rather bloodless. In cases associated with passive congestion, however, it may present the characteristic nutmeg appearance. Microscopical examination reveals in the liver cells fat droplets, usually of large size, which press the protoplasm and nucleus aside. The most marked change is toward the periphery of the lobule. In the degenerative types the liver may be smaller than normal. This reduction in size is often extreme in acute yellow atrophy. The fat droplets are usually minute, and the cell nucleus and the cytoplasm show evidence of degeneration. In many cases of fatty liver, both types of change are simultaneously present.

Symptoms.—The clinical picture is mainly that of the associated disease. Symptoms referable to the liver itself may be absent, but a sense of fulness and discomfort in the hepatic region is often noted. Jaundice, ascites, and pain are absent in the simple cases. Vague gastro-intestinal disturbances may occur.

Diagnosis.—The association of one of the causative conditions cited

above, with the presence of an enlarged, smooth, soft, and painless liver without jaundice should suggest fatty change. In obese subjects it may be difficult to determine the size of the organ. The history, the associated conditions, examination of the spleen, and the blood findings help to differentiate fatty liver from *cirrhosis, passive congestion, leukemic infiltration, amyloid disease,* and *displacements.*

Treatment.—The treatment is that of the primary or causative condition.

Amyloid Liver (*Waxy or Lardaceous Liver*).—Amyloid disease of the liver is not common in the United States and Canada. It occurs as part of a general degeneration, which is usually most marked in the spleen and kidneys. The disease most often attacks young people, usually as the result of long-continued tuberculous or other suppuration, or of syphilis. Occasionally it follows such wasting diseases as cancer, anemia, chronic arthritis, and other chronic infections. In syphilitic cases there is often tertiary ulceration, but amyloid disease may occur without suppuration. The view that it is of toxic origin is supported by suggestive results of experiments in which animals were injected with products of pyogenic bacteria or other toxic substances. Probably modern methods of treatment, by reducing the incidence of prolonged suppuration, are responsible for the relative infrequence of amyloid disease at the present time.

Morbid Anatomy.—The amyloid liver is uniformly enlarged, and in some cases attains four or five times its original size. It is smooth, firm, and cuts with resistance. The cut surface is pale and semi-translucent. Stained with Lugol's solution, the tissue appears rich mahogany brown in the amyloid areas. The median portions of the lobules are affected first, the process spreading both centrally and peripherally as the disease advances. Microscopically, it can be seen that homogeneous amyloid material is deposited in the capillary walls external to the endothelial lining. In more advanced cases there is also a deposit about the small branches of the hepatic artery.

Symptoms.—On clinical examination, the liver is found to be uniformly enlarged and smooth, but there is no pain or tenderness. The patient complains of no symptoms directly referable to the liver unless the enlargement is so great as to cause discomfort in the hepatic area. Symptoms of the primary or associated disease are usually present, however, and include general debility, wasting, and a pale cachectic appearance. The spleen is nearly always enlarged and firm, but there is no ascites. Jaundice does not occur.

Diagnosis.—The history of antecedent, or associated disease of a nature liable to cause amyloidosis, and the finding of an enlarged, smooth, firm, and painless liver and spleen should suggest the diagnosis. The condition must be differentiated from *fatty liver, cirrhosis, passive congestion, leukemic infiltration,* and *displacement.*

Treatment.—The treatment is that of the disease giving rise to the amyloid change. There are no remedies specific for the hepatic lesion. The development of amyloidosis of the liver does not affect the prognosis of the case, except that to some degree it is an index of the extent of the general disease.

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ANATOMICAL ABNORMALITIES AND DISPLACEMENTS OF THE LIVER

The main anatomical abnormalities of the liver are known as *corset liver* and *Riedel's lobe*. The cause of the former type is constriction of the lower thorax by tight clothing. Present-day fashions in women's dress have rendered this condition almost obsolete. The liver is usually dextroverted, so that the anterior border, passing from left to right, is horizontal in its medial portion, but proceeds almost vertically downward laterally. There is a shallow depression across the anterior surface of the liver, corresponding to the costal margin or to the waist line. Glisson's capsule over this depressed surface is thickened, and there may be marked atrophy of the liver substance. In extreme instances this area of the liver is reduced to a mere fibrous band separating the upper and lower portions.

Riedel's lobe is a tongue-like extension of the anterior margin of the liver. Sometimes it is painful and tender on pressure and may be mistaken for an inflamed and enlarged gall-bladder. It may also be erroneously diagnosed as a floating kidney, or a tumor of any of the structures of the right side of the abdomen. Riedel's lobe, when present, is frequently associated with disease of the gall-bladder and differential diagnosis is almost impossible.

Movable liver (floating liver, hepatosis) is a rare condition, which is usually part of a general visceroptosis. The suspensory ligament, which ordinarily is a mere reflection of the peritoneum from the upper surface of the liver to the under surface of the diaphragm, becomes greatly relaxed, and when the patient is erect may allow the liver to drop so that the upper hepatic surface is below the costal margin. The condition occurs most often in women, and the diagnosis is usually easy. No symptoms may be present, although the patients sometimes complain of a feeling of weight or dragging and vague digestive disturbances. Mechanical support, such as an abdominal belt or binder, is helpful in these cases.

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DISEASES OF THE BILE PASSAGES AND GALL-BLADDER

Catarrhal Jaundice (*Acute Catarrh of the Bile-ducts*).—Definition.—Catarrhal jaundice is usually the result of inflammatory swelling of the mucous membrane of the terminal portion of the common bile-duct. There may also be obstruction, due to inspissated mucus in the lumen of the duct. It occurs most frequently in children and young adults; in males more often than in females; and it may be epidemic.

Etiology.—The cause is usually some dietetic indiscretion, infection, or low-grade inflammation of the upper part of the digestive tract such as duodenitis or gastroduodenitis. Alcoholic excesses, exposure to cold, and profound emotional disturbances may also play an etiological rôle.

Morbid Anatomy.—Since catarrhal jaundice is rarely fatal, little is known about its morbid anatomy. It is generally believed that the mucous membrane is swollen and that the terminal portion of the common duct and ampulla of Vater are plugged with mucus. The primary lesion may, however, be in the liver itself. Duodenitis is usually associated with the condition. The bile is more viscous than normal, and contains desquamated epithelium, and occasional pus cells and bacteria. This suggests the presence of infection. Eppinger has described a proliferation of the lymphoid tissue in the ampulla of Vater which caused obstruction. Hurst and Willcox noted dilatation of the right heart after the catarrhal jaundice which was epidemic in Gallipoli during the Great War.

Symptoms.—The symptoms are varied. During the first few days slight jaundice, malaise, loss of appetite, coating of the tongue, nausea, sometimes vomiting, and constipation or diarrhea are evident. Some patients have a temperature of 100° or 101° F.

After this first phase the jaundice deepens, the stools become acholic, the urine tinged with bile, and the respiratory rate slow. Mental torpor, pruritus, and general lassitude and drowsiness are also characteristic of this stage. The pulse rate may fall to 40 or even 30. The liver may be slightly enlarged and tender; and the gall-bladder and spleen are sometimes palpable. As jaundice becomes more marked the digestive disturbances may become less severe, although they frequently persist if untreated.

Diagnosis.—The diagnosis is usually not difficult. At times the early manifestations of *acute yellow atrophy* simulate benign jaundice, but the onset of severe symptoms and the reduction of liver dulness soon makes differentiation possible. *Weil's disease* is marked by its acute onset, fever, and splenic enlargement. Jaundice without pain, which begins insidiously in middle-aged patients and becomes progressively more severe, is an indication of *malignant disease* and compression of the common duct. An *impacted stone* in the common duct causes colicky pain in the region of the gall-bladder, jaundice, fever, chills, and sweating. The *benign jaundice of early syphilis* usually becomes evident as the secondary symptoms (rash and sore throat) appear. Low grade *angiocholitis* may simulate catarrhal jaundice, but fails to disappear entirely.

Prognosis.—Catarrhal jaundice is never fatal. Recovery is complete and there are no common sequelæ. The condition rarely persists for more than six weeks, but may continue for three months or more. Suitable treatment often shortens the course of the disease.

Treatment.—Early treatment should be designed to relieve the gastro-

intestinal catarrh. Calomel may be given to keep the bowels open, but salines are preferable. The fluid intake may be abundant, but the diet should be restricted. Small quantities of milk diluted with lime-water or Vichy water are permissible at first. Later, when the gastro-intestinal symptoms have disappeared and the appetite returns, milk gruel, toast, rice pudding, and custards may be taken. Fats should be avoided. Cereals, vegetables, and fruits that are easily digested should form the bulk of the diet.

The catarrh of the upper part of the digestive tract may be relieved by gastric and duodenal lavage with mild alkalies such as bicarbonate of soda. The duodenal tube permits systematic duodenal disinfection and biliary drainage, and makes possible cleansing of the terminal portion of the common duct. Such lavage may also dislodge the material causing obstruction.

Lyon has shown that the introduction of 25 per cent. magnesium sulphate solution into the duodenum relaxes the sphincter of Oddi and allows free flow of bile from the gall-bladder and bile-ducts. By the early use of this method the duration of the disease can be greatly shortened.

Colonic lavage and intestinal antiseptics such as salol, benzonaphthol, and bismuth salicylate are sometimes desirable.

The pruritus may be treated by local application of carbolic acid (1 :60), or if necessary by hypodermic injection of atropin (gr. 1/100).

Acute Suppurative Cholangitis.—Definition.—Suppurative cholangitis is a purulent inflammation of the bile-ducts, which is almost always associated with inflammation of the gall-bladder.

Etiology and Occurrence.—This condition may follow acute infections such as pneumonia, influenza, and typhoid fever; it may be a manifestation of severe cholecystitis, and is the most serious complication of cholelithiasis. Occasionally it is produced by the pressure of neoplasms upon the ducts. Suppurative cholangitis also accompanies pylephlebitis with diffuse and multiple abscesses of the liver. Whatever the primary cause, suppurative cholangitis is the result of infection with pyogenic bacteria such as the *Streptococcus pyogenes*, *Bacillus coli*, *Bacillus typhosus*, *Staphylococcus aureus*, or *Pneumococcus*.

Morbid Anatomy.—The lesion usually involves the intrahepatic bile-ducts as well as the common duct and gall-bladder. There is often great dilatation and thickening of the involved ducts. The lumen contains pus mixed with bile. Small abscesses may be present in the periportal areas of the liver, and there may be extensive pericholangitis and hepatitis. The liver as a whole is enlarged and soft. The suppurative process may extend through the duct of Wirsung to the pancreas, or may invade the portal vein, the peritoneum, or diaphragm.

Symptoms.—The symptoms of suppurative cholangitis are those of jaundice and severe infection, as well as of the underlying condition. Chills, fever, swelling, and localized tenderness over the liver and gall-bladder are frequently associated with the presence of stones and the occurrence of colic. Loss of appetite and also of strength and weight is not uncommon, and secondary anemia often develops. Septicemia is not an infrequent symptom; blood-cultures are often positive. There is leukocytosis, intermittent fever, jaundice, colic, and rigors, and sweats suggestive of severe sepsis.

Complications.—The suppurative process may spread to other organs.

In some instances pyemia has developed, and abscesses in the lungs and other parts of the body. Endocarditis may also complicate the syndrome.

Diagnosis.—The onset of fever, chills, sweating, leukocytosis, enlargement and tenderness of the liver, and jaundice in a patient who has had gall-stones, disease of the biliary tract, or severe general infection should immediately suggest suppurative cholangitis. *Abscesses of the liver* and *suppurative pylephlebitis* may sometimes simulate the condition very closely.

Prognosis.—The prognosis is usually bad. If it is possible to establish suitable drainage into the duodenum, or, by surgical means, through the gall-bladder or ducts, the patient may recover.

Treatment.—Immediate operation and evacuation of pus is necessary. Drainage of some sort is essential. Non-surgical drainage may be sufficient in some cases. Stimulation should be resorted to when necessary, and the patient's diet made as simple as possible.

Chronic cholangitis may occur as a sequel to acute cholitis. It varies from a mild catarrh of the bile-ducts to a severe and persistent suppurative infection.

Usually there is more or less obstruction of the bile passages with subsequent dilatation of the ducts. The gall-bladder is dilated and as a result of the stasis and inflammation gall-stones often form. Jaundice is a characteristic symptom. Complete obstruction is usually referable to a malignant growth. When the obstruction is incomplete, the bile passages and gall-bladder are not so much dilated; but even with partial obstruction a majority of the cases are associated with cholelithiasis.

The symptoms of chronic angiocholecystitis are sometimes quite characteristic. In typical cases the patient is subject to recurring attacks of chills, fever, and sweats. The student should remember that these symptoms do not necessarily mean suppuration in the biliary passages.

Acute Infectious Cholecystitis.—Etiology.—Acute cholecystitis rarely develops alone; more frequently it is part of a general cholangitis, or results from the trauma produced by gall-stones. The immediate cause is bacterial infection. The association of acute cholecystitis with appendicitis is of interest in the light of recent theories which suggest that lesions in the appendix exert a reflex influence upon the gall-bladder and sphincter of Oddi.

Bacteriology.—The organisms most commonly found in the gall-bladder belong to the *colon-typhoid group* (56 per cent. of cases). The *Bacillus paratyphosus*, *Staphylococcus* (9 per cent.), *Pneumococcus* (9 per cent.), and *Streptococcus viridans* (2 per cent.) are less frequently present. *Bacillus fecalis alkaligenes* has also been found. The organisms are carried to the gall-bladder in the blood-stream, or ascend from the duodenum in the bile.

Morbid Anatomy.—Acute cholecystitis is of several types, each being a development of a less severe form. In *simple catarrhal cholecystitis* the gall-bladder is usually distended, its walls are tense and swollen, and the mucous membrane congested. Desquamation or even superficial ulceration may take place. Lymphocytic and polynuclear infiltration occurs. In the *subacute type* the villi stand out as yellow specks and give the lining of the gall-bladder a "strawberry" appearance. Complete or partial blocking of the cystic duct with stones or inflammatory edema predisposes to *suppurative inflammation*. In this more serious form the mucosa of the gall-bladder

is covered with a mucopurulent or purulent exudate, and shows patches of exfoliation or gangrene. The muscular coat is infiltrated with leukocytes, and the serous coat dulled with a deposit of fibrin. Empyema of the gall-bladder may result. The process may develop into a *gangrenous cholecystitis* which is characterized by extensive necrosis of the wall of the gall-bladder. If perforation of the gall-bladder occurs, local or generalized *peritonitis* may result.

Symptoms.—The *mild catarrhal form* may cause no symptoms except slight indigestion, but when the infection is severe, paroxysmal pain and tenderness develop in the region of the gall-bladder. Rigidity of the right upper rectus, nausea, vomiting, fever, and distention follow. Sometimes the gall-bladder is palpable. The number of leukocytes in the blood is increased. Jaundice does not result unless the hepatic or common duct is obstructed. The symptoms of the *suppurative form* are more severe. Prostration is marked, and signs of peritoneal irritation are usually present. There is often generalized abdominal pain, caused by the association of the branches of the celiac axis and the vagus; pain over the gall-bladder at the intersection of the right costal cartilage and the border of the right rectus; and not infrequently the pain is referred to the right shoulder. The spleen may be enlarged. Albumin is present in the urine. Perforation causes profound shock and death unless operative measures are employed immediately.

Diagnosis.—As primary acute cholecystitis is rare, the condition is usually complicated by the symptoms of some underlying condition such as diffuse cholangitis, cholelithiasis, or chronic cholecystitis. The history of the illness permits differentiation from *perforation of a gastric or duodenal ulcer*. *Acute appendicitis* may be distinguished by the location of the pain and tenderness, the previous history, and the absence of a palpable mass in the region of the gall-bladder. If *Riedel's lobe* is prominent, however, differentiation may be difficult.

Prognosis.—The catarrhal form of acute cholecystitis usually subsides within a week or ten days, and the patient recovers completely. Sometimes the process becomes chronic. The more severe forms may prove fatal unless there is surgical intervention.

Treatment.—The treatment of acute catarrhal cholecystitis is essentially that of acute cholangitis. Rest in bed, restriction of the diet, and the application of poultices or stupes to the hepatic region are adequate measures. Lyon's method of duodenal tube drainage is apparently helpful at times. Suppuration or empyema of the gall-bladder demands immediate surgical treatment.

Chronic Cholecystitis.—Etiology.—Chronic cholecystitis may follow the acute form, or it may be slow and insidious from the onset. It is very frequently associated with cholelithiasis. The immediate cause is infection with an organism of low virulence, such as the *Streptococcus viridans* or *Bacillus typhosus*.

Morbid Anatomy.—The lesions vary from those characteristic of the so-called "strawberry gall-bladder" to a wide-spread inflammation of all the coats. The epithelial lining may be entirely denuded and replaced by cicatricial tissue. The gall-bladder may be distended with mucopus, or thick bile, but often it is small and sclerotic and surrounded by dense adhesions. Gall-stones are present in about 70 per cent. of cases. The regional

lymph-glands are enlarged. The head of the pancreas may be indurated. Whether the infection spreads to the pancreas by way of the lymphatics or along the bile-duct and the duct of Wirsung is not definitely decided, but the lymphatic route is the more probable.

Symptoms.—The symptoms of chronic cholecystitis and cholelithiasis are practically identical, and clinical examinations often fail to demonstrate whether gall-stones are present or not. Many patients complain merely of vague digestive disorders, flatulence, belching, acid eructations, and a sensation of weight or oppression in the upper abdomen. The symptoms of indigestion are often indistinguishable from those of appendicitis. Ingestion of food does not give relief. There may be intervals of varying length in which the patient is free from symptoms. These are followed by attacks of pain, chilliness, and a slight rise of temperature, thought to be due to reinfection or to spasms of the gall-bladder caused by the irritation of calculi. Pain simulating biliary colic may occur, however, in the absence of gall-stones. Palpitation and precordial oppression may be due to flatulence or to absorption of toxins from the gall-bladder. Secondary infection of the joints, endocardium, and other susceptible tissues may follow chronic cholecystitis.

Diagnosis.—Persistent digestive disturbances, especially during or after middle age or in obese individuals, should arouse suspicion of disease of the gall-bladder. Recently the gall-bladder has been roentgenographically visualized by the administration of certain halogen salts of phthalein. This is known as cholecystography and is of undoubted value in the diagnosis of gall-bladder disease.

Treatment.—The treatment of chronic cholecystitis is essentially that of cholelithiasis. A simple diet, combined with the daily taking of salines is about all medical treatment has to offer. Surgery is indicated when the symptoms are severe and persistent or when adhesions between the gall-bladder and pylorus or duodenum interfere with proper functioning of the gastro-intestinal tract.

Carcinoma of the Gall-bladder and Bile-ducts.—Primary malignant disease of the gall-bladder is by no means rare and is almost always carcinomatous in type. Sarcoma is very seldom seen. Gall-stones are associated with carcinoma of the gall-bladder or biliary tract in about 87 per cent. of cases; and many observers claim that between 5 and 10 per cent. of the cases of chronic cholelithiasis become malignant. Women are more subject to carcinoma of the gall-bladder (4 to 1) than men, and men are more susceptible to primary malignancy of the ducts.

Morbid Anatomy.—The growth is usually a *carcinoma simplex*, occasionally an adenocarcinoma. Rarely squamous-celled carcinoma is seen. Secondary carcinoma of the gall-bladder is not as common as primary.

Symptoms.—As the symptoms which commonly precede the development of *carcinoma of the gall-bladder* are those of chronic cholecystitis or cholelithiasis, it is usually very difficult to determine the exact onset of malignancy. Usually a smooth firm tumor which becomes gradually nodular can be felt in the region of the gall-bladder. This, in association with dull pain and jaundice in a patient more than fifty years of age, should always arouse suspicion of carcinoma. The mass is usually tender, and there may be either persistent or paroxysmal pain. Jaundice occurs in the majority of cases as the result of extension of the process to the liver or of

involvement of the bile-ducts. In the later stages there is anemia, loss of weight, and general impairment of health and strength.

The first manifestation of *carcinoma of the bile-ducts* is a steadily deepening jaundice. There may be colicky pain, but in many cases this symptom is entirely absent. The gall-bladder is distended and the liver enlarged.

Prognosis.—Death usually results from carcinoma of the gall-bladder within seven or eight months. Carcinoma of the bile-ducts proves fatal, because of cholemia, within a few months.

Treatment.—Medical treatment is merely palliative. Excision of the growth is rarely possible because diagnosis in the very early stages is impossible. Exploratory laparotomy may, however, demonstrate the feasibility of such treatment.

Cholelithiasis (*Gall-stones, Biliary Calculus*).—Etiology and Occurrence.—Gall-stones are generally believed to form as the result of infection, stasis of bile, or alterations in the chemical composition of the bile. Certain recent experimental observations have shown, however, that it is possible for calculi to develop when all of these supposedly essential conditions are lacking.

Infection.—Since the gall-bladder can be so readily infected through the blood or by ascending or descending processes, it seems not unlikely that it frequently may be the seat of chronic infection. Nevertheless it is probably sterile in more than 50 per cent. of the cases of cholelithiasis seen at operation. Rovsing believes that infection follows rather than precedes the formation of calculi, while Rosenow thinks that the gall-stone is probably produced by the *Streptococcus*. Calculi composed of bile-pigment and calcium are found frequently in patients with a history of cholecystitis. *Colon bacilli, Typhoid bacilli*, and the *Pneumococcus* and *Staphylococcus* are all possible infecting agents. The typhoid bacillus, which has been obtained in pure culture from gall-stones, is much less commonly encountered than was formerly believed.

Stasis of Bile.—Stasis is an etiological factor, chiefly because it permits the bile to become unduly concentrated in the gall-bladder. Rous and McMaster state that the concentration of pigment in the bile of the gall-bladder may be ten times that of the entering bile; and Rovsing says that the bile present in the gall-bladder at operation is between five and ten times as concentrated as that which escapes after operation. It is possible that the physiological stasis which may follow lack of normal stimuli in the duodenum might develop into pathological stasis as the result of irregular habits.

Changes in the Composition of the Bile.—Chauffard states that the liver cell is responsible for the chemical composition of the bile, its content of cholesterol, and the secretion of bile-salts which render cholesterol soluble. When toxins (due to constipation, etc.) are continually absorbed from the portal blood the quantity of cholesterol in the bile increases, and the quantity of salts which render this substance soluble decreases. Consequently, calculi form, if there is stasis or infection of the gall-bladder. Chauffard believes that infection with the *Bacillus typhosus* causes the formation of biliary calculi only in so far as it causes a condition of hypercholesteremia during the stage of convalescence. The markedly high incidence of cholelithiasis in women who have been pregnant is likewise explained by the fact that in the last months of pregnancy and for some time after delivery

hypercholesteremia is marked. McNee has demonstrated that an increase of the quantity of cholesterol in the blood is associated with an increase of the quantity of this substance in the bile. Some families are doubtless predisposed to a so-called "cholesterol diathesis." Rosenbloom has pointed out that patients with cholesterol stones usually do not give a history of infection.

Predisposing Factors.—*Age.*—Gall-stones are found at autopsy in between 5 and 10 per cent. of cases. A large proportion are seen in individuals more than forty years of age, and very few in patients less than twenty years old; but such statistics are misleading, for they give no idea of the time of formation of the calculi. It is quite possible that some stones are formed in youth when infectious diseases occur frequently.

Sex.—Cholelithiasis attacks women much more often than men, perhaps because of conditions due to pregnancy, puerperal infection, sedentary habits, and tight lacing.

Diet.—Although improper balance of the diet has long been regarded as a cause of the formation of biliary calculi, there is no direct evidence upon which to base this belief. The fact that a diet rich in lipoids increases the cholesterol content of the blood and bile may, however, afford some support for this belief. The high incidence of cholelithiasis on the Continent, particularly in Germany and Austria, is probably explained by the prevailing constipation, excessive ingestion of fat, and sedentary habits.

Character of Biliary Calculi.—The number, composition, size, and structure of gall-stones varies greatly. Otto reports finding 7802 in one patient. The largest stone reported in the literature is that found by Richter; it weighed 110 gm. Most stones are faceted or rounded. They are of five types: (1) solitary pure cholesterol calculi which are usually rounded, white or yellowish in color, and on section present a radiating crystalline structure; (2) laminated cholesterol stones with an outer shell of bilirubin-calcium material, which are often faceted and composed of alternate layers of cholesterol and lime salts; (3) stones composed of cholesterol and bilirubin-calcium mixed together, usually small, rather soft and friable, and non-crystalline; (4) pure bilirubin-cholesterol stones which are always small but vary in size from mere grains to forms as large as a pea; (5) rare forms composed of amorphous cholesterol, calcium carbonate, or foreign bodies such as fragments of worms.

According to various observers stones form within a period varying from about two to six months.

Symptoms and Signs.—The symptoms and signs of cholelithiasis vary with the position of the calculi, and are in some measure caused by the mechanical action of the stones. Certain manifestations are, however, common to all types of the condition. Although symptoms may be entirely lacking, it is more usual for vague digestive disturbances such as fulness or oppression in the upper abdomen, nausea, acid eructations, flatulence, and chilliness after eating to develop as early manifestations. Persistence of such symptoms in a patient more than forty years of age should always suggest the possibility of disease of the gall-bladder or biliary tract. Heartburn is very common. These generalized symptoms are aggravated by pregnancy. Quite commonly the recurring attacks of indigestion with pain and tenderness over the gall-bladder are separated by intervals of comfort. While these vague symptoms, which frequently persist for many

years, may be the only manifestation of cholelithiasis, more distinct evidence of the presence of gall-stones usually appears.

A *stone in the gall-bladder* acts reflexly and not mechanically and therefore produces no symptoms of obstruction. Unless there is profound irritation and infection of the wall of the gall-bladder, colic does not develop. All the signs and symptoms are digestive in nature ("the inaugural" symptoms of Moynihan) and result from activity of the vagus and sympathetics. As they frequently simulate those of ulcer or chronic appendicitis, diagnosis is very difficult. Aërophagia, vagotonia, and pyloric spasm are the most common. The irregularity and unusual association of belching, eructation, fulness, and dull pain are characteristic.

Stones which occlude the cystic duct cause non-obstructive biliary colic. The hepatic ducts, which are more or less parallel to the cystic duct, are often compressed, and the gall-bladder is frequently dilated. Lawson Tait reported finding a gall-bladder which contained 11 pints of liquid. At first the contents are composed of bile and mucus or mucopurulent material, later of mucus or mucopus alone. Atrophy as well as the various manifestations of chronic cholecystitis is liable to follow extreme dilatation.

A *calculus in the common duct* most frequently causes obstruction near the termination of the duct. The usual gall-stone colic and all the signs of obstructive jaundice are characteristic manifestations of this condition. Complete obstruction is rare, but when it does occur may produce jaundice of long duration. The gall-bladder is not enlarged, but the biliary ducts are, in most cases, markedly dilated. The spleen may be palpable. Bile is absent from the stools and present in the urine. This type of stone may lead to suppurative cholangitis.

A movable *calculus in the ampulla of Vater* often causes ball-valve obstruction. When this is associated with infection, so-called hepatic intermittent fever results. The jaundice usually deepens after each paroxysm of pain and vomiting. Such attacks may be very severe and may resemble those of malaria. The temperature rises to between 102° and 105° F. There is always danger of pancreatic as well as hepatic involvement.

Intestinal obstruction by gall-stones is not as rare as has been generally believed. Fitz reports that of 295 cases of intestinal obstruction 23 were due to biliary calculi.

Gall-stone Colic (Biliary Colic, Hepatic Colic).—Gall-stone colic usually begins abruptly and, in the majority of cases, at night about four, five, or six hours after the last meal. It is due to migration of calculi into the ducts; to spasm of the muscular coat of the gall-bladder as the result of acute inflammation; and to distention and stretching of the gall-bladder by bile. The *pain* is paroxysmal, lancinating, and although chiefly localized in the epigastrium and right upper quadrant of the abdomen, may radiate in all directions. It is frequently felt on both sides, and spreads to the back; throughout the abdomen where it shifts from side to side; to the right shoulder; and occasionally through the chest and down one or both arms. Usually the patient becomes very much excited, and may pace the floor, press the fists into the abdomen, lean over the back of a chair, or roll from side to side in agony. It is characteristic for *sweat* to drench the clothing. The *marked aërophagia* often aggravates the symptoms. As the pain decreases, *tenderness* over the gall-bladder becomes noticeable, and the day after an attack there may be unmistakable evidence of *subicterus* in the

sclera, or of *general icterus*. The *urine* may be darkened by bile pigments, and the *feces* passed after the paroxysm may be acholic, although that passed during the attack of pain is usually normal in appearance. It is claimed that there is *slight fever* in more than 50 per cent. of cases, but this is rarely a pronounced feature of the syndrome. It is probably caused by concomitant cholecystitis or cholangitis. The *pulse* is usually normal or increased only a little, and there is *slight leukocytosis*. The fact that bile is present in the vomitus at the beginning of an attack is evidence that the biliary flow is not obstructed. The paroxysms may last only a few hours, or may persist for several days with remissions. The length of the intervals between attacks varies, but in most cases becomes progressively shorter and shorter. Occasionally marked cardiac involvement causes collapse, faintness, or even fatal syncope during a paroxysm.

Complications.—The more important complications of cholelithiasis are *biliary fistulæ* opening into the colon, duodenum, hepatic duct, peritoneal sac, pleural sac, or skin; *perforation into the peritoneum* as the result of acute cholecystitis or empyema of the gall-bladder; *intestinal obstruction* caused by a stone which enters the duodenum through a fistula and becomes impacted usually in the ileocecal valve; the formation of *adhesions* to the stomach, first and second portions of the duodenum, and hepatic flexure of the colon; *chronic cholecystitis; pancreatitis* due to extension of inflammation along the duct of Wirsung; *hepatitis;* and occasionally *stricture of the bile-ducts.*

Diagnosis.—During the early stages, when the symptoms are chiefly those of vague digestive disturbances, a diagnosis of cholelithiasis is usually impossible. The stones may, however, in rare instances be felt through a thin or lax abdominal wall. In between 10 and 50 per cent. of cases they are demonstratable by the *x*-ray. By improved methods a larger percentage of stones are now radiographically demonstrated. The determination of the functional efficiency of the gall-bladder and its visualization by cholecystography are likewise important in the diagnosis.

Acute biliary colic is easily recognized. If the patient has had previous gastric upsets and other symptoms of acute or chronic cholecystitis followed by a sudden attack of colicky pain in the upper right side of the abdomen, chills, fever, and severe gastric disturbances, cholelithiasis should always be suspected. Jaundice, however slight, makes the diagnosis certain.

Peptic ulcer, renal colic, or *acute intestinal obstruction* may cause confusion, but are easily differentiated after the crisis has passed. The pain of renal colic begins in the lower abdomen or back, radiates to the genitals, and is frequently accompanied by dysuria, hematuria, and frequent micturition. *Intestinal colic* and *lead colic* are distinguished by the history of constipation and exposure to lead, the location of the pain in the central or lower portion of the abdomen, the blue line on the gums, and the blood-picture. Complete obstruction by a biliary calculus sometimes simulates *carcinoma* of the head of the pancreas, bile-ducts, or adjacent parts of the bowel or stomach. Such malignant disease, however, usually begins insidiously, is painless, and manifested by cachexia and enlargement of the gall-bladder.

Prognosis.—Cholelithiasis is rarely fatal, but such accidents as rupture or perforation of the gall-bladder, acute obstruction of the intestines with stone, and acute hemorrhagic pancreatitis make the prognosis uncertain.

Treatment.—*Prophylactic.*—Since hypercholesterinemia, infection of the gall-bladder, and stasis of bile appear to favor the formation of gall-stones, individuals who have had acute cholecystitis, particularly if they are fat, should restrict the intake of fat and eggs; avoid overeating; wear loose clothing, and take a reasonable amount of out-door exercise. Whenever possible, foci of infection about the tonsils, sinuses, and teeth should be removed. By means of duodenal intubation the presence in the bile of any pathogenic organisms may be determined. If the *colon bacillus, Streptococcus*, or *Staphylococcus* are thus discovered, *vaccine* may be given in order to increase the resistance to these bacteria. The bowels should be kept free and plenty of water ingested. Occasional visits to spas or springs, such as Saratoga, Bedford, or Vichy, are desirable.

Medical.—In the medical treatment, which is both direct and symptomatic, *control of the diet* is of great importance. None of the foods taken should contain much cholesterol. Immediately after an acute attack little food should be administered. Skimmed milk alone at first, and then with cereals, and milk soups made with some of the starchy vegetables are permissible. Later the patient may have milk, cereals, fruits, and vegetables, and in some cases such short-fibered meats as poultry and fish (except salmon, mackerel, and herring). Eggs in every form are to be avoided because the yolk contains a great deal of cholesterol. Pork products, fat meat, and fried food, as well as substances with a high nucleoprotein content, like sweetbreads and brain, are also to be strictly avoided. Alcoholic beverages, spices, acids, fatty cheeses, and rich dressings must also be eliminated from the diet.

Hydromineral cures are often recommended for amelioration of the condition as well as for its prevention. Evian, Contrexville, Grande Grille, and even Carlsbad waters, in addition to those suggested in the paragraph on Prophylaxis, are helpful. It is quite as satisfactory, however, to administer small amounts of exsiccated sulphate, bicarbonate and phosphate of soda dissolved in hot water ($\frac{1}{2}$ teaspoonful in 1 tumbler of water before meals). Epsom salts (1–4 drams once a day) may be given to advantage for protracted periods.

The salicylates and hexamethylenamin are said to exert an *antiseptic action on the bile*. Salicylate of soda or aspirin may be given in 5-grain doses three times a day after meals: hexamethylenamin in 5-grain doses for a limited period and resumed after a reasonable interval.

Olive oil (100 c.c. or more per day) mixed with a little lemon juice is a preparation which is supposed to stimulate the excretion of bile. *Glycerin* (1 teaspoonful after meals) has also been recommended. *Benzoate of soda* (up to 20 grains per day) is often given with equal quantities of salicylate of soda. Calomel (in fractional doses with salines), mineral oil, agar, mild laxatives, and such *cathartics* as cascara, aloes, podophyllum, compound extract of colocynth, and phenolphthalein, combined with *antispasmodics* like belladonna, are all useful in certain cases.

For relief of the *acute attacks and colic* certain measures are absolutely necessary. Heat must be applied to the abdomen by means of hot compresses, turpentine stupes, or flaxseed poultices; hypodermic injection of morphin ($\frac{1}{4}$-gr. doses repeated as necessary), with or without atropin, is required to relieve the excruciating pain; and if the stomach is tolerant, spirits of chloroform, spiritus etheris compositus, or aromatic spirits of

ammonia with bicarbonate of soda prove beneficial. For milder attacks a suppository or even a rectal injection of codein ($\frac{1}{4}$–$\frac{1}{2}$ grain) or heroin hydrochlorid ($\frac{1}{2}$ grain) and extract of belladonna ($\frac{1}{2}$ grain) with analgesine (5 grains) may be given. *Gastric lavage* occasionally gives great comfort. As the colon is usually distended with gas, a simple enema or mild irrigation often brings relief. In most cases it is best to keep the patient quiet, administer a carminative and antispasmodic by mouth, apply heat to the abdomen, and give a simple enema. If this does not allay the pain, morphin ($\frac{1}{4}$ grain) and atropin (1/100 grain) should be injected at once.

For the itching associated with the jaundice, local applications of carbolic lotion 1 : 60 are useful. Menthol ointment sometimes gives relief when it is applied to the skin.

As gall-stones cannot be dissolved, it is generally realized that medication merely allays the active manifestations of cholelithiasis. Therefore, whenever the symptoms do not yield to medical treatment, and inflammation and infection of the gall-bladder and biliary tract persist, or when the general health is failing, operation is the best form of therapy.

Surgical.—In a large majority of cases operation effects cure. W. J. Mayo reports that in 16,980 operations upon the biliary tract the mortality was 2.8 per cent. Crile states that the proportion of deaths following cholecystectomy is about 2.5 per cent., that following cholecystotomy 5.4 per cent. These figures form a basis for the growing popularity of cholecystectomy. Operations on the common duct increase the mortality to between 8 and 10 per cent. The most common cause of death after operation is hepatic insufficiency. Nearly all recent discussions emphasize the necessity of adequate preparation of the patient for the operation. The clotting time of the blood should be determined, the tetrachlorphthalein test for liver function performed, calcium administered, and, if necessary, transfusion of blood carried out.

A second operation may be necessary in about 8 per cent. of cases. Stones reform in about 10 per cent. The causes of failure are continued infection, re-infection, formation of more stones, unrecognized stone, hernia, stricture of the ducts, hepatitis, pancreatitis, and the formation of adhesions, with consequent deformity of adjacent organs.

Stenosis and Obstruction of the Bile-ducts.—*Stenosis* of one of the bile-ducts occasionally follows ulceration after the passage of a gall-stone.

Obstruction.—The commonest cause of obstruction of the bile-ducts is an impacted gall-stone. Obstruction of the bile-ducts may also be caused by foreign bodies or intestinal parasites. Obstruction by pressure from without is most frequently due to carcinoma of the pancreas. Occasionally it may be caused by chronic adhesions secondary to cholecystitis or pyloric ulcer.

Symptoms.—The most striking symptom of stenosis is jaundice. The liver may or may not be enlarged. With incomplete obstruction, notably from gall-stones, there may be chills, fever, and sweats. Permanent obstruction of the common duct eventually causes death.

Diagnosis.—The diagnosis of obstruction of the bile-ducts can usually be made with ease from the mere presence of jaundice. The determination of the cause of the obstruction, however, is more difficult. The history of attacks of pain followed by jaundice and intermittent fever is very suggestive of gall-stones. In obstruction due to carcinoma jaundice is constant

and increases in severity. In carcinoma the liver is also more apt to be enlarged.

Treatment.—This will depend upon the cause of the obstruction. In any condition the treatment is usually surgical.

Congenital Obliteration of the Bile-ducts.—A congenital obliteration of the bile-ducts is rare. Rolleston believes it results from primary cirrhosis of the liver caused by poisons which enter the fetus in the umbilical vein. These produce a descending and obliterative cholangitis of the extrahepatic ducts, which become obstructed more readily than in later life on account of their comparatively small lumen. Others believe that the condition is due to a developmental aplasia which causes secondary biliary cirrhosis. The spleen is enlarged and the pancreas shows some fibrosis about the ducts.

Symptoms.—Clinically the disease is characterized by a deep and progressive jaundice, beginning at birth or appearing several days later. The stools are clay colored and the urine is deeply stained with bile. The blood coagulation time is prolonged and hemorrhages occur into the skin, mucous membranes, and from the umbilical cord. Emaciation soon appears and most of the patients die after one to six months.

Diagnosis.—The diagnosis depends on the association of deep jaundice in the newborn with enlargement of the liver and spleen. The possibility of umbilical infection must be ruled out. Syphilis must be excluded by investigation of the history and by the Wassermann test. The clay-colored stools are a means of differentiation from *icterus neonatorum*.

Treatment.—Medical treatment can do no more than relieve the symptoms. As surgery can give relief, theoretically at least, in about 16 per cent. of cases, the infant should be operated on as soon as the diagnosis is made.

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Diseases of the Pancreas

Because of the many important functions of the pancreas, some of which are associated with those of other parts of the alimentary tract, diseases of the pancreas were for many years confused with those of the stomach, liver, and intestinal tract. The modern history of the study of the diseases of the pancreas begins with the contribution of Friedreich published in 1857. The knowledge of such phases of the pathology of the pancreas as gangrene, fat necrosis, hemorrhage, acute and chronic inflammation, and the relation of the pancreas to diabetes gradually increased during the following three decades. Chiari in 1876 described a case of sequestration of a gangrenous pancreas. Balser in 1882 was the first to describe accurately fat necrosis as seen in the pancreas and adjacent fatty tissue. American pathologists added to the subject when in 1886 Draper described pancreatic hemorrhage as the cause of sudden death, and Reginald Fitz in 1889 clearly established the clinical entity of acute pancreatitis. In the same year von Mehring and Minkowski published their classic paper on the relationship of diabetes mellitus to the internal secretion of the pancreas.

Since that time the elaborate monographs of Oser, Opie, and Mayo Robson, the work of Sweet, and the recent epoch-making contribution of Banting in perfecting insulin in the treatment of diabetes, have brought the subject to its present position of importance in both medicine and surgery.

Pathogenesis.—Before classifying the diseases of the pancreas it is essential to point out certain facts in the physiology and pathology of the pancreas. The pancreas has both an internal and an external secretion. The former has to do with the metabolism of carbohydrates which is apparently the one vital function of the pancreas. The external secretion, collected by a duct system and emptied as pancreatic juice into the duodenum, contains the proferments or zymogens which when activated have to do with the

digestion of proteins, fats, and carbohydrates. The most potent stimulant of the production of pancreatic juice is secretin which is absorbed from the duodenum and carried by the blood to the pancreas. The two constituents of the pancreatic juice most important in the study of pancreatic disease are the trypsinogen and steapsinogen. These are inactive in the ducts and parenchyma of the organ, but when activated are powerful ferments. The normal activating agent for trypsinogen, which transforms it at body temperature immediately into trypsin, is the enterokinase produced by the cells of the mucosa of the small intestine. Steapsinogen, on reaching the duodenum, is normally transformed by some constituent of the bile into the fat-splitting ferment, steapsin.

Infection or trauma may cause activation of the zymogens of the pancreatic juice in the gland itself or in the adjacent tissues, and thus give rise to the characteristic and pathognomonic lesions of protein and fat autodigestion which are seen at operation or autopsy, and to the various grades of inflammation described as acute pancreatitis. Acute lesions are the result of the action of both these ferments; but the distressing and often fatal disturbances which accompany such changes are due to the proteolytic digestion of the blood-vessels and living protein of the pancreas and adjacent tissues. Thus the action of trypsin is all important in the etiology of these acute lesions. From the experimental work of Sweet and others it would seem that in the acute lesions trypsinogen is transformed into trypsin by an activating substance produced by autolysis of the pancreatic tissue. An injury sufficient to produce local necrosis and subsequent autolysis of pancreatic tissue, with activation of trypsinogen, may result from direct trauma, hemorrhage (as in apoplexy of the pancreas), or acute bacterial infection. Delezeune first demonstrated the presence in bacteria of an activating substance similar to enterokinase in its action on trypsinogen.

Morbid Anatomy.—It is evident that the degree of trypsin and steapsin digestion determine the pathological findings at various stages of acute pancreatitis. Lesions vary from an edema of the pancreas and retroperitoneal tissues and peritoneal exudate to extensive hemorrhage into the gland and peripancreatic tissue, with necrosis of the gland and more or less fat necrosis in the pancreas and peritoneal fat, according to the stage and severity of the disease. In these lesions the activating agent of the steapsinogen is apparently independent of the activator in the bile. It is the presence of typical areas of fat necrosis—round pearly white spots in the subserosa of the mesentery, in the peritoneal fat, and in the interlobular fat of the pancreas—that is always indicative of pancreatic disease. The absence of such fat necrosis does not, however, rule out the possibility of acute pancreatitis. Fat necrosis, a dirty sanguineous exudate in the peritoneum, and edema, induration, and enlargement of the pancreas are the most common abnormalities found at operation. Usually all three and always at least two of these changes are seen during acute pancreatitis.

If autolysis of the gland causes progressive hemorrhage, necrosis and gangrene of more or less of the pancreas result. Infection may be followed by varying degrees of edema and suppuration, and by the formation of abscesses.

Symptoms.—In the severe types of pancreatic disease associated with necrosis and autolysis of the pancreas and hemorrhage into the gland, there is an acute and fulminating toxemia, often sufficiently severe to cause death within a few hours. To Sweet belongs the credit of focusing the attention

of the profession in this country on this dreadful intoxication—the *Pancreasvergiftung* of the Germans. As a result of his experiments, corroborated by many investigators, he has demonstrated that when the sterile excised pancreas of one animal is placed in the peritoneal cavity of another animal of the same or a different species, the animal into which the pancreas is transplanted invariably dies with symptoms of profound toxemia. Immediate autopsy reveals evidence of fat necrosis, an irritative peritonitis, most marked about the transplanted pancreas which is softened and disintegrating, and a dirty peritoneal exudate. The animal's own pancreas is not pathologically changed. Sweet maintains, and very logically, that the pancreatic juice of the transplanted organ is the cause not only of autolysis of the host's tissue but also of the profound intoxication. Whether this poison be elaborated by the destruction of the animal's own pancreas or within the transplanted pancreas, the effects are the same.

It is the quantity of this poison which determines the severity of the constitutional symptoms of acute pancreatitis and explains why in some cases the constitutional symptoms are so overwhelming when the anatomical changes are so slight.

PANCREATITIS

Acute Pancreatitis.—Definition.—The term "acute pancreatitis" includes the hemorrhagic, suppurative, and gangrenous types.

Occurrence.—The disease appears to be more common in adult males who eat and drink heavily. The fact that in many patients the onset comes one or two hours after a heavy meal is explained by recalling that the pancreas is most active at that time, and that any injury, such as a small hemorrhage or distention of a duct, would favor the action of trypsin and autolysis. The disease is frequently associated with cholecystitis and cholelithiasis. A calculus lodged in the papilla of Vater may dam up the bile until it is forced back into the pancreatic duct. Cases reported by Opie and subsequently by many other observers have clearly demonstrated this. In a series of patients at the Presbyterian Hospital the fulminating hemorrhagic form, the suppurative type, and abscess of the pancreas were associated with a cholangitis and chronic cholecystitis.

Symptoms.—In the hemorrhagic and diffuse suppurative types the onset, which is sudden, is characterized by agonizing and constant pain in the epigastrium or about the umbilicus, with severe nausea and vomiting and symptoms of collapse. A rapid pulse of low tension and an ashy cyanosis are not uncommon. Extreme tenderness over the pancreas, extending into the costovertebral angles when the retroperitoneal tissue is involved, are characteristic. The muscular rigidity is not as marked as in perforated ulcer of the stomach or duodenum. In the patients with the less fulminating lesions obstipation is common, and the most frequent error in diagnosis is to consider this acute intestinal obstruction.

The constant agonizing pain, the symptoms of collapse, and the paralytic ileus have been explained as the result of stretching of the celiac plexus

which is involved in the edematous peripancreatic tissue; but the experiments of Sweet point to the localized peritonitis and profound toxemia as the cause of the fulminating symptoms.

Diagnosis.—Intestinal obstruction, acute peritonitis due to the perforation of an ulcer or diseased appendix, and acute cholecystitis are the conditions most frequently confused with acute pancreatitis. In any obese individual giving a history of a heavy meal with alcoholic excesses, or of gall-stone attacks, or of the recurrent digestive disturbances of chronic cholecystitis, acute pancreatitis should be suspected. When such histories are given by patients with extreme or even moderate tenderness over the pancreas, there is sufficient evidence for diagnosis.

Treatment.—It is to be noted that the lesions most often confused with acute pancreatitis are those demanding prompt surgical intervention. Therefore exact diagnosis is chiefly of academic interest, and an exploratory operation should be performed at once. The least delay may prove extremely hazardous to the patient. There is absolute necessity for drainage of the infection as well as of the pancreatic ferments, for the pancreatic juice is rendered constantly more active by progressive autolysis of the gland. Therefore, celiotomy with drainage to the pancreas, and decompression of the bile-ducts, if jaundice is present, should be performed as soon as possible. Modern methods of transfusion and saline infusion, which can be carried on during and after operation, have improved treatment to a great extent. In the more recent cases the slow infusion of a very high dilution of adrenalin and the hypodermic administration of pituitrin have been used to combat the extremely low blood-pressure and symptoms of collapse.

Chronic Pancreatitis.—The pathological change characteristic of chronic pancreatitis is an increase in the interstitial connective tissue which replaces more or less of the parenchyma of the gland. Opie has pointed out two histological types of chronic inflammation: (1) the interlobular, usually associated with lymphangitis, in which the increase of fibrous tissue is limited to the tissue between the lobes; and (2) the interacinar, in which the new growth of connective tissue invades the interacinar spaces, replacing the parenchyma and involving the islands of Langerhans. In the interlobular variety the lesion is more apt to be limited to a part of the pancreas, especially to the head, where it is most commonly associated with a descending infection of the biliary tract. The interacinar type usually involves the entire gland and is frequently associated with *diabetes mellitus*.

The increase in connective tissue may be caused by an arteriosclerotic or endarteritic condition of the vessels; by a syphilitic process, or by blocking of the ducts. Most often it is the result of long-standing and persistent infection of the lymphatics of the pancreas which communicate freely with those of the biliary tract, duodenum, and transverse colon.

Symptoms and Diagnosis.—Epigastric distress, bloating and belching, epigastric tenderness, constipation or diarrhea, and irregular jaundice are symptoms common to chronic pancreatitis. They may also occur with lesions of the biliary system. If, however, in addition the patient suffers from a sense of fulness and the stools are large, foul, and fatty, and contain undigested meat fibers, or if there is sugar in the urine, a diagnosis of chronic pancreatitis is probably correct. The decrease or absence of pancreatic ferments in the duodenal fluid is added evidence. The fluid should be obtained by the Einhorn tube and examined immediately.

Carcinoma of the pancreas is most difficult to differentiate from chronic pancreatitis. Irregular jaundice, a history of biliary colic, and absence of an enlargement of the gall-bladder suggest chronic pancreatitis; while jaundice of gradual onset, steadily increasing, without a history of biliary colic, and a palpable pear-shaped gall-bladder point to carcinoma of the head of the pancreas. The newer technic of gastro-intestinal fluoroscopy makes it possible to differentiate between *gastric carcinoma* and chronic pancreatitis in spite of the similarity of symptoms.

Treatment.—For the interacinar type, associated with glycosuria, the usual medical measures employed in diabetes may be used. Because of the digestive disturbances, fats and proteins have to be largely eliminated from the diet. Pancreatic extract is of real benefit in some cases, and may be given in doses of 0.3 to 0.6 gm. in salol-coated capsules after meals.

For the common interlobular type of pancreatitis the same treatment should be tried; but surgery should be employed to remove any focus of infection, such as chronic cholecystitis or some biliary infection. In many cases carefully watched at the Presbyterian Hospital removal of the infected gall-bladder or drainage of an infected common duct has resulted in permanent recovery from the symptoms referable to the diseased pancreas. The results at the Mayo Foundation and at the Lankenau Clinic have for many years proved the efficacy of surgery in this disease.

There are a certain number of cases that even at operation cannot be differentiated from carcinoma of the head of the pancreas. For these cholecystgastrostomy or cholecystduodenostomy is necessary. Permanent relief and disappearance of jaundice are the therapeutic diagnostic tests.

Pancreatic Calculus.—Pancreatic calculi are rare and are usually found accidentally at autopsy. Their presence is practically never recognized during life. They are usually small, are composed of calcium phosphate and calcium carbonate, and in most cases are situated in the main pancreatic duct. They are usually associated with chronic pancreatitis.

Cysts of the Pancreas.—Gulecke's classification of pancreatic cysts is the most comprehensive. He divides them into:

Adenocystomata or cystic new growths which are multilocular as a rule, and most often found in the tail of the pancreas.

Retention cysts, the most common form, which develop when the ducts are obstructed, and are usually associated with a chronic pancreatitis.

Degeneration cysts which result from softening and cystic degeneration of pancreatic tissue caused by necrosis or hemorrhage.

Pseudocysts which are characteristically located outside the parenchyma of the pancreas and, as a rule, occupy the lesser sac. These frequently form after injury to the pancreas, and contain at first changed blood, later a clear, glairy fluid composed largely of pancreatic juice.

Symptoms and Diagnosis.—Since Gussenbauer first diagnosed the condition in 1882, the symptomatology has been carefully studied, but even today it is not clear cut. Pain in the epigastrium or in the left upper quadrant, the development of a palpable tumor in the region of the epigastrium or umbilicus, and symptoms of indigestion similar to those of chronic pancreatitis are the common manifestations. Because of the position of such cysts above the stomach or between the stomach and colon, gastric and colonic inflation with air may aid diagnosis. The *x*-ray examination of the abdomen which has been inflated with a few hundred cubic centi-

meters of oxygen or sterile air may demonstrate the cyst. A steadily enlarging mass in the upper abdomen is the most characteristic sign.

Treatment.—Aspiration is a bad practice. An exploratory incision under novocain anesthesia is desirable, both to establish the diagnosis suggested by the other evidence, and to evacuate the contents if the enlargement proves to be a cyst. Suture of the opening of the cyst to the abdominal incision (so-called marsupialization) is then advisable in order to prevent accumulation of fluid within the cyst.

Tumors of the pancreas are usually malignant and almost always carcinomatous. Adenocarcinoma is the most frequent type. Carcinoma usually occurs in the head of the organ and rapidly involves the common bile-duct and adjacent lymph-nodes.

Symptoms.—The symptoms vary with the location of the tumor, but great weakness, loss of weight, and extreme anorexia are always present.

If the tumor is in the head, jaundice appears, as a rule, gradually. Unless the gall-bladder has been previously inflamed, it enlarges to an easily palpable, pear-shaped mass as the jaundice deepens. There may be glycosuria, but it is rare. The presence of a palpable mass in the region of the pancreas is also very infrequent. The pain and tenderness vary with the amount of involvement of the celiac plexus. The pain is characteristically of a severe boring or grinding type and extends through to the back. During the jaundice the stools are foul, clay colored, and fatty. The blood-clotting and bleeding time are prolonged as the jaundice deepens or persists.

Diagnosis.—As has already been stated, differentiation between these tumors and chronic pancreatitis is almost impossible. A persistent deepening jaundice, coming on gradually without pain, in an elderly individual with a palpable gall-bladder is almost certainly a sign of carcinoma of the head of the pancreas.

Treatment.—In the late stages no treatment gives relief. In the early stages, the patient may be spared several weeks of great emaciation and pruritus by anastomosis between the gall-bladder and stomach or duodenum. In 5 patients seen by the writer, a diagnosis of carcinoma of the head of the pancreas was made during operation; all were relieved of symptoms for twelve to thirty-six months by a cholecystenterostomy. Cases that eventually prove to be chronic pancreatitis illustrate the difficulty of the differential diagnosis and the advantage of applying surgery to an otherwise incurable condition.

Allen O. Whipple.

Diseases of the Peritoneum

General Considerations.—The peritoneum is a connective-tissue membrane arranged in complex folds enclosing a cavity. It is abundantly supplied with blood and lymphatic vessels, which enter and leave it through the extra- or subperitoneal layer made up of more or less loose connective tissue. On its inner surface there is a layer of one thickness of endothelial cells which are now known to completely cover it, without the presence of the open spaces called stomata which formerly were believed to make a direct com-

munication between the cavity and the outwardly draining lymphatics (MacCallum).

The peritoneum is one of the great serous sacs of the body (*e. g.*, the pleura, pericardium, joints, etc.). In the male, it is completely closed from the external world, but in the female, there is a direct external communication through the vagina, the uterine canal, and the fallopian tubes.

It possesses the mechanical function of furnishing smooth apposed surfaces which permit ease of movement to the various organs and structures which the sac covers. It also has the physiological function of a secreting membrane and is capable of active absorption. Normally the exchange of fluid secreted on its endothelial surface and absorbed therefrom is nicely balanced so as to moisten this surface, and thus make for greater ease of movement. This balance no longer obtains under pathological conditions. Absorption from the peritoneal sac takes place both by the lymphatics and the blood-stream and is very rapid. While it has not been proven experimentally that fluids or solids can pass into the peritoneal lymphatics with an entirely undamaged endothelial covering, such must happen physiologically, otherwise there would be no change in the normal fluid that the sac always contains. It has been shown, however, that when an infection takes place, the first response is an exfoliation and proliferation of the endothelial cells, and the lymphatics thus being opened absorption is prompt and extensive. Under these conditions fluids, bacteria, and solid particles are found in the mediastinal lymph-nodes in a few minutes after their introduction into the peritoneal sac (Buxton). By this route they readily get into the thoracic duct and are poured into the blood-stream. There is some evidence to show that absorption also takes place directly into the blood-vessels. The protective function of the peritoneum is manifest by the fact that infections in the abdominal parietes rarely break through the peritoneum into the interior of the cavity, and also by the fact that intraperitoneal infections are in many instances rendered inactive by the peritoneal reaction.

The parietal peritoneum lines the under surface of the diaphragm, the posterior and anterior abdominal parietes, and the pelvic floor, while the visceral portion is closely attached to the surface of all the intra-abdominal viscera, in fact, makes the external coat or layer of many of them—*e. g.*, the stomach, intestines, liver, and the fundus of the uterus and of the bladder. The total surface of the peritoneum equals or is greater than that of the skin, and this great surface when extensively inflamed may permit of an overwhelming absorption of toxic material. This serous sac is subject to the same pathological changes as its fellows, but inflammation of the peritoneum is much more frequent and of more clinical importance because of its intimate relation with the gastro-intestinal viscera, and their normal content of pathogenic bacteria.

PERITONITIS

The peritoneum is one of the most common sites of inflammation, not because it is especially susceptible to infection, but because it is so often subject to attack. While peritonitis is a definite pathological entity, its

manifold clinical aspects are largely the outcome of the underlying disease or of the effect produced by that disease on the intraperitoneal viscera. These symptoms are so prominent that one is easily misled into thinking that they are due entirely to the peritonitis. They are, in fact, often produced by the lesion causing the peritonitis or by associated lesions which result from the peritonitis itself.

The peritoneum reacts to irritation in varying degree and extent. Both acute and chronic inflammation of the peritoneum may be localized or diffuse, according to the extent of the lesion. Bacteria or their toxins are, in most instances, the irritating agents, although blood, urine, and bile, even when not infected, may cause peritoneal inflammation. *Endogenous peritonitis* results from infection by organisms from the abdominal viscera; *exogenous*, from infection by organisms carried to the peritoneum from without by the blood-stream, trauma, or operation, or, in the female, by the genital tract. The endogenous form is by far the more common. *Primary idiopathic peritonitis* does not occur (unless by way of the fallopian tubes), but the peritoneum may become infected through the blood-stream from insignificant foci in distant parts of the body. Not infrequently such foci cannot be found, and the peritonitis is the outstanding feature of the syndrome, although it is secondary and not primary. In the female, bacteria, particularly pneumococci, may reach the peritoneum through the fallopian tubes and cause peritonitis without evidence of inflammation in the genital tract.

Acute Peritonitis.—Definition.—Acute peritonitis is acute inflammation of the peritoneum.

Etiology.—Acute peritonitis results from bacteria or their toxins gaining entrance to the free surface of the peritoneum. The source of the bacteria is usually the hollow viscera of the abdominal cavity. These organs are constantly filled with bacteria which often have considerable virulence, and are, therefore, always prepared to attack the host. Disease of the appendix, the intraperitoneal genital organs, the gall-bladder, or any part of the gastro-intestinal tract may be the antecedent cause of peritonitis. Such diseases may lead to a complete perforation of a hollow viscus (the appendix, gall-bladder, or intestine) which allows the infecting bacteria direct access to the peritoneum. Perforation, however, is not a requisite for the passage of bacteria from the lumen to the peritoneal surface of the hollow organs, for this may occur through a damaged wall which is still anatomically intact. This method of infection is an accepted cause of much of the chronic, localized fibrous peritonitis in the colonic area and, less often, of acute peritonitis without perforation. Hematogenous infections of the peritoneum are occasionally derived from foci of infection elsewhere in the body. This is rare, however, in comparison with the primary disease.

Any pyogenic micro-organism may be the cause of peritonitis. Most commonly the colon bacillus is the predominating organism because it is abundant in the gastro-intestinal tract, grows luxuriantly both *in vivo* and *in vitro*, and is capable of overgrowing and killing less robust organisms. The streptococcus, Staphylococcus aureus, pneumococcus, gonococcus, and Bacillus pyocyaneus are also causative agents.

Morbid Anatomy.—At the very outset the endothelial cells of the peritoneal covering undergo marked proliferation and assume a phagocytic function. At the same time an outpouring of coagulable lymph takes place,

the smooth covering of the peritoneal surface is lost, and adhesions form between contiguous surfaces of the parietes and visceral contents. During this phase a greatly increased absorption is taking place and the bacteria are carried, with an excess of phagocytes and polymorphonuclear leukocytes, into the lymph-stream and to the regional lymph-nodes.

If the dosage or virulence of the infecting agent is not overwhelming the process is localized and an abscess forms. In this process the omentum plays an important part. The great peritoneal apron, composed of loose connective tissue and fat, well vascularized, and with ample lymph drainage, is essentially a peritoneal free lance which possesses almost unlimited excursion of movement within the cavity. Whether drawn by chemotaxis or actually pushed by the intestines, it rapidly moves to the point of attack and wraps itself around the area so as to limit the spread of infection. As the inflammatory process progresses the subperitoneal tissues, the muscular coats of the viscera, and the omentum all become thickened and densely adherent one to the other. Vascular thrombosis and gangrene may supervene. The outcome depends on the relative virulence of the attack and the strength of the defense. If the organisms prove too toxic the localization is lost and extension takes place. If the defense is sufficiently great the abscess is completely walled off, and may, in rare instances, become sterile.

The lesions of spreading or diffuse peritonitis are not different from those just described except that from the start the activity of the attacking organisms is greater than the defense. Adhesions are less manifest. The pus is more abundant and spreads along lines of least resistance. If uncontrolled by operation this spreading process may continue until the entire peritoneal cavity and even the under surface of the diaphragm are infected. This is called generalized peritonitis. In a certain number of cases the defense mechanism seems to break down entirely and the inflammation with the production of pus spreads with great rapidity from the original focus (*e.g.*, the appendix). Neither fibrin nor adhesions are present; indeed sometimes in severe streptococcus peritonitis even pus is absent, and there is only an intense dry injection of the peritoneum throughout the whole sac. This is known as dry peritonitis. Death often supervenes in twenty-four or forty-eight hours, and at autopsy no other changes in the peritoneum are found.

In acute suppurative peritonitis there are important concomitant pathological lesions. First among them is paralysis of the intestinal muscularis with consequent intestinal stasis or obstruction. The degree of stasis is usually proportional to the extent of peritoneal involvement of the intestine; that is, muscular paresis develops where there is visceral peritonitis, but the peristaltic power remains intact beyond this area. The paresis may eventuate in total paralysis with complete local obstruction of that segment of the bowel. Probably both nervous factors and actual inflammation of muscle-fibers are responsible for this paralysis. Mechanical intestinal obstruction may also result from the inflammatory adhesive bands which bind and kink the bowel so that the fecal contents cannot be propelled forward. Residual abscesses may develop if the patient survives the more acute stage of a spreading or general peritonitis. Such lesions are found most often in the pelvis and in the subhepatic and subphrenic regions. The latter probably are often expressions of a spread by the lymphatics and not by direct continuity.

During the development and progress of acute peritonitis there is a constant absorption of the products of the infection and probably of bacteria by both the lymphatics and the blood-stream. The diaphragmatic peritoneum is particularly active in such absorption, as are also the lymphatics leading directly to the thoracic duct.

Symptoms.—The symptoms of acute peritonitis *per se* are so closely bound up with those of the underlying disease that it is often impossible to determine where the one leaves off and the other begins. On the contrary, in many conditions the symptoms are only manifest when peritonitis has resulted, and no matter what the origin of the infection, once it has attacked the peritoneum, a fairly definite picture is presented. This picture, however, is greatly modified by associated conditions, by the virulence of the attacking organisms, and by the comparative resistance of the peritoneum.

There are certain symptoms of acute peritonitis which may be enumerated with advantage: *Suddenness of onset, pain, vomiting, disturbance of the bowels, anxiety*, and *prostration*. These are associated with definite physical signs, characteristic *posture* and *facial expression, dryness* of the *tongue, elevation* of *temperature* and *pulse, leukocytosis, change* in the *contour* and *mobility* of the *anterior abdominal wall, local tenderness*, and *muscular rigidity*. Many of these symptoms and signs occur in non-peritoneal affections, but the rule is to find them nearly *all* present in acute peritonitis, and together they make a clinical picture which is not readily overlooked. All these symptoms and signs are not present to the same degree, but it is noteworthy that the more severe and extensive the peritoneal infection, the more severe are the symptoms and the more marked are the physical signs.

Acute suppurative peritonitis begins with the sudden onset of *severe pain*, usually near the site of the lesion which causes the peritonitis. In acute appendicitis, however, the pain first appears not infrequently in the mid-epigastrium and is not felt in the cecal region for some hours. The pain is of a boring, burning type, almost continuous, but with exacerbations of an excruciating character. As long as the peritonitis remains localized the pain is also local, but as the process spreads the pain becomes more diffuse and follows with a fair degree of accuracy the progress of the inflammatory process. Should a large part of the peritoneal cavity be invaded suddenly, as in perforation of a full stomach, the pain is so extensive and fearfully acute that the patient often falls to the ground. As the disease advances and general sepsis supervenes, the pain is lessened and one may be led into the mistake of believing the process is subsiding. Any movement increases the pain and therefore the patient lies quietly on the back with the knees and thighs flexed to relax the abdominal wall. The respiration is, as far as possible, thoracic.

Vomiting is an almost universal symptom of acute peritonitis. It usually occurs once shortly after the beginning of the attack when the stomach is emptied of its contents. Later, when the peritonitis has become diffuse, with considerable intestinal paralysis, there occurs a second stage of vomiting. The vomitus now is really regurgitated gastric, intestinal, hepatic, and pancreatic secretions. It is raised in comparatively small amounts and occasionally in greater quantity, without violent retching. It becomes more and more foul and dark until it is almost black. The material may even resemble fecal vomitus, although the actual fecal particles ejected in intestinal obstruction are rarely present. This type of vomiting is evidence

of very extensive peritonitis and practically complete intestinal paralysis, with consequent blocking of some segment of the intestine. It is a most unfavorable symptom and, as a rule, is the forerunner of rapid death.

There are frequently one or more loose movements from the bowel coincident with or shortly following the onset of the attack, and thereafter obstipation or even complete obstruction. Enemata may remove some gas and a small amount of fecal matter from the colon, but aside from this nothing is passed, and cathartics, which are absolutely contra-indicated, are ineffectual. When intestinal paralysis ensues there is complete obstruction. This plays a determining part in fatal cases. Occasionally septic diarrhea, accompanied by an almost continuous discharge per anum, persists throughout the disease; its cause is not clear. The urine is usually scanty, highly colored, and contains considerable indican. Frequent urination may be a symptom, but occasionally there is urinary retention.

The patient feels sick, troubled, and anxious. He seems to sense impending disaster. The sensorium is unusually alert, although there is marked prostration, with muscular weakness. In conditions that prove fatal this prostration becomes extreme. In the later stages the patient is dull and apathetic, sometimes with low delirium and muscular twitching. He lies on his back, with legs and thighs flexed; avoids all movement; and, with diaphragm fixed, limits breathing to the smallest possible excursion of the thoracic wall. The eyes are bright, keen, and inquiring, but there is an expression of anxiety, worry, and pain. The face in very acute conditions is pale, with a hectic flush. In advanced cases there is a peculiar, pinched, drawn expression with a dusky cyanosis, which, once seen, is almost never forgotten. The tongue is dry and coated in the middle, but is often glazed on the edges. As the condition progresses the tongue may become dry, rough, and hard. Thirst is most intense and the taking of fluids by mouth does not alter the condition.

Both the *temperature* and *pulse rate* are above normal, but the change in pulse rate is a more reliable guide than the degree of fever. The temperature rises, as a rule, to 100° or 102° F., but often the fever is not marked. There may be hyperpyrexia in fulminating cases; in advanced cases, as death approaches the temperature may not rise above 102° F. In general, the higher the temperature, the more severe and extensive is the peritonitis, but the reverse by no means universally holds. On the other hand, it is only in exceptional cases (very old, debilitated, or cachectic patients) that the pulse rate is not markedly raised. It usually rises rather suddenly toward 110, and if the process is extending, the rate may become still higher. When the peritonitis is severe, the pulse rate approaches 150. The pulse volume is small and thready. Death eventually results from failure of the heart and vasomotor system. A drop in the pulse rate may always be considered as a favorable symptom except when it takes place before the peritonitis has developed and some hours after the onset of the disease which anteceded the peritonitis. On the other hand, marked ups and downs in the temperature curve may occur without any significance whatever so far as the course of the disease is concerned.

A *leukocytosis* is always associated with acute suppurative peritonitis. The average leukocyte count is 15,000 to 20,000 (82 to 87 per cent. polynuclears). This increase in the number of leukocytes is very prompt and can be found within an hour or two after the onset of peritonitis. It is usually

maintained until death or until the disease is well under control. A leukocyte count of more than 20,000 indicates either infection of a very severe grade or an unusually favorable reaction. When the figures are lower than 12,000, and when polynuclear cells show less relative increase than the total number of cells, there is cause for apprehension (Handley, Gibson).

Physical Signs.—Changes in abdominal contour, local tenderness, and muscular rigidity are the physical signs which provide the best diagnostic evidence of acute suppurative peritonitis. Attention has already been drawn to the posture which permits relaxation of the abdominal muscles and limitation of movement by fixation of the diaphragm in respiration. Careful inspection usually demonstrates that the abdominal wall over the starting-point of the peritonitis seems to be "fixed," *e. g.*, the lower segment of the right rectus abdominis in appendicular peritonitis. When diffuse peritonitis develops rapidly (after duodenal perforation, for example) the whole abdominal wall is retracted and fixed (so-called "scaphoid abdomen"). Late in the disease, distention appears as evidence of intestinal paresis. Palpation should reveal quite definite muscular rigidity or resistance, and tenderness. The rigidity can most certainly be felt if the palpation is so gentle and skilful that it elicits no pain; rough palpation with a cold hand causes discomfort and voluntary abdominal contraction even when peritonitis is not present. *Reflex abdominal rigidity* is the most reliable of all the physical signs of peritonitis. Its presence is best determined by preliminary palpation over a part of the abdomen not believed to be involved. This serves the double purpose of gaining the confidence of the patient and of establishing the normal resistance of the muscles. If the procedure be then carried out over the entire abdomen, passing from one part to another, a definite and easily noted reflex response of the abdominal muscles can be felt over the area where peritonitis exists (Ashhurst). The more extensive the peritonitis, the more extensive and, as a rule, the more marked is the resistance. For example, if appendicitis be the primary disease, the resistance is at first restricted to a limited area in the right lower quadrant; as the process extends, usually into the pelvis, suprapubic resistance develops. If, however, an acute duodenal perforation releases a large amount of infectious material into the peritoneum, a characteristic, board-like resistance covers the whole right side and probably the suprapubic area, and in a few hours may extend upward along the left gutter.

Abdominal *tenderness* may be due to the original disease or to the subsequent peritonitis. If it be extensive in area it is evidence of peritonitis. The degree of tenderness is a very fair guide to the extent of peritoneal involvement. *Cutaneous hyperesthesia* (so-called "Head area") may be present, and is best demonstrated by drawing a pin point over the suspected area. More pain is felt over the inflamed region than over the corresponding part of the opposite side (Head). Pain may also be elicited by picking up and pinching the skin, taking care not to produce any internal pressure. Percussion, as a rule, fails to give valuable information in acute spreading peritonitis, although it may, by showing regions of dulness, locate an abscess. Rarely is there sufficient fluid to cause dulness in the flanks. Intestinal obstruction caused by either mechanical changes or paralytic ileus is followed by distention of the bowel which gives the characteristic tympanic note on percussion. Such tympany is usually found above the umbilical line and is most marked in the epigastrium, both the colon and

the stomach being enormously distended. This may eventuate in the obliteration of liver dulness, so that this sign does not of necessity indicate a perforative lesion with free air in the peritoneal cavity.

Auscultation often gives valuable information. Audible passage of gas through the intestinal coils is an indication that the muscularis is not completely paralyzed. Total absence of this sound when the upper abdomen is distended and tympanitic is a grave sign, as it means that peristalsis is lost and intestinal obstruction imminent. In old, debilitated patients with no power of resistance all symptoms and signs may be absent.

Diagnosis.—In typical cases there is rarely any difficulty in making the diagnosis. When, however, acute peritonitis is hematogenous, follows the passage of infecting bacteria through the fallopian tube, or is subsequent to acute obstruction or severe abdominal trauma, the condition may be very difficult to recognize. Often, too, the free blood liberated by rupture of a tubal pregnancy may so irritate the peritoneum that the resulting acute symptoms and signs are confusing.

Peritonitis is a late complication of intestinal obstruction just as intestinal obstruction is a late complication of peritonitis. In the late stages the absence of a reliable history may make it impossible to determine which disturbance was primary. Traumatic conditions often present a diagnostic problem of extreme difficulty in the early stage. Severe injury to the abdominal wall may, by tearing a mesenteric vessel or injuring the liver or spleen, evoke intraperitoneal hemorrhage. The blood and injury together often irritate the peritoneum and produce the same local symptoms and signs as an infectious irritant. The constitutional symptoms of hemorrhage, if marked, may lead to a correct diagnosis. Furthermore, peritoneal irritation by blood alone tends to decrease rather than to increase, whereas if rupture of a hollow viscus infects the peritoneum, the evidence of peritoneal infection grows stronger from hour to hour. In many cases the exact condition can only be determined by operation.

Not infrequently in children, and occasionally in adults, pulmonary infection may simulate peritoneal infection. All the local signs point to the peritoneum as the site of trouble, and evidence of pulmonary change is absent or very indefinite. As a rule, however, both the respiration rate and the leukocyte count are higher in pneumonia than in peritonitis, and the facies is quite different in the two diseases. Unless the condition is critical, diagnosis may be delayed until the appearance of the physical signs of pneumonia, usually within twenty-four hours, but it should be remembered that needless laparotomy is less dangerous than delay in the treatment of serious peritonitis. A radiograph of the chest may be of diagnostic value.

Prognosis.—If left to itself acute general peritonitis is almost invariably fatal. If treated by well-established medical and surgical methods at its inception, however, death results only from the fulminating type or when for some reason the patient's resistance has been markedly lowered. Every hour of delay is a definite hazard. The peritonitis which follows appendicular or gall-bladder disease is often localized for a time, and consequently more amenable to surgical intervention than other types, although it is caused by particularly virulent organisms. Acute perforation of the stomach or duodenum, on the other hand, is apt to release a large amount of infectious material in the peritoneal cavity without a localizing reaction. Exogenous peritonitis, particularly that caused by a blood-borne

hemolytic streptococcus, is the most dreaded form, for it is the one most apt to be fatal. Since the peritoneum possesses a very real and definite power of resistance to most of the bacteria which commonly attack it, the prognosis depends in most instances on the amount of help given this resistance by removing the source of infection and providing proper drainage.

Treatment.—The treatment of acute, suppurative peritonitis is surgical. The source of the infection must first be found and removed, and adequate drainage then provided. The questions of when to delay operation (following the plan of treatment laid down by Ochsner in certain cases) and which operation is best must be answered by the surgeon.

The use of catharsis when peritonitis is suspected is fraught with danger. Administration of morphin before diagnosis is established may render the problem more difficult. If nausea or vomiting are present the ingestion of food or even water is contra-indicated. Otherwise the administration of water is important and may be given by the rectum or under the skin. Emptying the colon by enemata and colonic irrigation with tap-water often give great relief and may make the pain tolerable without morphin. Application of dry heat over the abdomen is also comforting in many instances. Gastric lavage often reduces the nausea. The patient should be kept as quiet as possible. Transportation to a hospital, if it is necessary, should be carried out with the utmost gentleness. After the diagnosis has been made, morphin may be given with great advantage while arrangements for operation are being made.

Localized peritonitis may be either acute or chronic. The acute form usually appears as an abscess, the walls of which are formed partly by inflammatory exudate and partly by agglutinated viscera, the mesentery, and the omentum or the parietal peritoneum.

The *symptoms* are chills, fever, sweats, and prostration, with localized pain, tenderness, and muscular rigidity. The leukocyte count is elevated. The abscess may heal spontaneously, but it more frequently ruptures into one of the hollow organs, or into the general peritoneal cavity. It may discharge externally through the abdominal wall.

Subphrenic Abscess.—*Definition.*—A subphrenic abscess is a collection of pus between the diaphragm and the viscera immediately below it.

Etiology.—The most frequent causes of this condition are acute appendicitis, gastric ulcer, infections of the gall-bladder, and suppuration in the liver. Less common causes are abscess of the spleen or kidney, carcinoma of the stomach, tuberculosis of the spine, and suppurative processes, such as empyema or abscess of the lung in the thoracic cavity.

A subphrenic abscess on the right side is usually referable to disease of the appendix or liver; on the left side to peptic ulcer. According to Stevens about one-third of all subphrenic abscesses contain gas.

Symptoms.—The symptoms of subphrenic abscesses vary considerably with the primary cause. The onset may be abrupt or gradual. In the former case there is severe pain and vomiting, often of bile-stained or bloody material. The respiration is embarrassed and there are such symptoms of suppuration as chills, irregular fever, and loss of weight. In the less acute form the local signs are not so marked. There may, however, be bulging of the lower ribs, or unilateral swelling in the abdomen with deep-seated tenderness. There are symptoms of septic infection—fever, rapid pulse, chills, pallor, loss of weight, and leukocytosis. If the abscess contains

pus only, there is dulness on percussion; if it contains both pus and gas, there is a tympanitic area at the base of the thorax which changes in outline as the patient changes position.

Diagnosis.—A subphrenic abscess, which does not contain air, is very apt to be mistaken for *empyema.* When air is present the physical signs are often those of a *pneumothorax;* under these conditions marked depression of the liver and bulging of the ribs may be of diagnostic assistance. The *x*-ray is also of great value in the diagnosis of this condition. Exploratory puncture through the thoracic wall may also be of material aid.

Prognosis.—The prognosis in subphrenic abscess is not good. Osler states that only 20 per cent. of patients recover. Bernard reports a mortality rate of 37.5 per cent. in 64 cases treated surgically.

Treatment.—The treatment is surgical. Spontaneous recovery occasionally occurs when the abscess ruptures and discharges through the skin or into one of the hollow viscera.

Other Forms of Acute Localized Peritonitis.—The most frequent cause of *localized peritonitis in the male* is appendicitis. The abscess may form in the pelvis or in the iliac region. It frequently lies on the psoas muscle between the cœcum and the terminal portion of the ileum and its mesentery.

Acute pelvic peritonitis is a frequent sequel of inflammation about the uterus and fallopian tubes. Gonorrhea, puerperal sepsis, and tuberculosis are the commonest causes.

Chronic peritonitis is of two types: fibrous and serous. The *fibrous* form results when mildly irritating substances destroy the endothelial covering of the peritoneum. This evokes a flow of coagulable lymph from the raw surface which unites it to other surfaces similarly involved. Later, connective tissue is laid down and the two surfaces are joined by a fibrous band. The endothelial cells in turn cover this band and it becomes vascularized. An adventitious peritoneal band is the result. Such lesions assume the form of strings, narrow ribbons, or broad sheets. They have a tendency to contract and thus produce deformities which result in fixations and obstructions in the intestinal tract with marked disturbance of function. This form of peritonitis may also be the terminal stage of acute suppurative peritonitis from which the patient has recovered. So-called postoperative adhesions are an expression of the same process. This type of chronic peritonitis is quite common and is usually more or less localized.

In the *serous* form there is an outpouring of clear serous fluid into the peritoneal cavity which may or may not be accompanied by fibrous peritonitis. This manifestation of the disease is commonly associated with tuberculosis or carcinoma of the peritoneum, but may also be the result of trauma, chronic nephritis, and cardiac or hepatic disease.

Symptoms.—If the fibrous adhesions interfere with free movement of the gastro-intestinal tract or occlude the bile passages, symptoms of these complications become manifest. Collection of fluid in excessive amounts causes distention of the abdomen which may similarly interfere with visceral function. The symptoms are then due to these disturbances and indicate the diagnosis. Pain of a colicky nature is recurrent, nausea and vomiting may be present, and constipation or even chronic obstruction may develop. Such peritonitis most often involves the colon, particularly the right colon. If the adhesions are marked around the hepatic flexure they may interfere

with the pylorus and duodenum, and cause symptoms suggestive of an ulcer, or may affect the gall-bladder and ducts and produce symptoms simulating those of cholecystitis.

Treatment.—The treatment of this type of peritonitis must overcome the disturbance of function. By regulation of diet, the proper use of laxatives, and colon irrigations, the symptoms may often be ameliorated. Since the probable cause is low-grade infection from the intestinal tract these measures may result in actual cure. In some instances surgery must be resorted to, but the effect of operation is not as favorable as could be desired. The treatment of chronic serous peritonitis is removal of the fluid (see section on Ascites).

Tuberculous Peritonitis.—See section on Tuberculosis.

Pneumococcus Peritonitis.—The pneumococcus may reach the peritoneum through the female genitalia or by the blood-stream. The former path is much the more common. There is no evidence that the route of infection may be through the gastro-intestinal tract, although this is considered possible by some writers. The disease is much more common in girls than in boys. It occurs in girls between the ages of three and seven among the poorer classes where cleanliness is lacking. Before the third year the vaginal orifice is not freely open and after the seventh year the reaction of the vaginal secretion changes from alkaline to acid. There is a definite seasonal variation in the disease, the incidence being higher during the warmer months when children are scantily clad and sit on the ground where the vagina may become infected with the pneumococcus in infected sputum. This form of peritonitis in young girls is a primary disease, the peritoneum alone being the seat of attack. Undoubtedly the organism sometimes reaches the peritoneal cavity via the blood-stream, but peritonitis is a very infrequent complication of either lobar or bronchopneumonia, although in both, pneumococcus bacteriemia is common.

Morbid Anatomy.—Pathologically, pneumococcus peritonitis is very similar to other forms of suppurative peritonitis. It may occur in a more or less circumscribed area, or it may be quite diffuse from the start. The pus, which is at first thin and albuminous, later becomes like that of pneumococcus empyema—thick, yellowish, and containing much fibrin. The presence of so much fibrin tends to cause adhesion of peritoneal surfaces, and when the starting point is limited, a local abscess may develop. In most cases the pelvis is the first region attacked.

Symptoms.—The symptoms are those already described under acute generalized peritonitis. They tend to regress as the localizing process becomes established.

Diagnosis is based on the sex and age, the absence of preceding intra-abdominal disease, the tendency toward involvement of the lower abdomen at the onset, and the presence of other foci of pneumococcic infection in the throat, ear, or lungs. Positive diagnosis is possible only when the infecting organism is obtained at operation.

Prognosis.—The prognosis is serious in the more acute forms, but good when the condition develops slowly and is chronic.

Treatment.—Operation is necessary in most cases as soon as diagnosis has been made. In the chronic type, operation may be advantageously delayed until the process has become localized.

John A. Hartwell.

TUMORS OF THE PERITONEUM

Tumors of the peritoneum, except endothelioma, are always secondary. Any tumor, either benign or malignant, which involves one of the viscera covered by the peritoneum, may implicate the peritoneum in its growth. *Carcinoma* not infrequently spreads throughout the peritoneum and produces a condition known as peritoneal carcinosis. The stomach and ovary are the most common sources of this disease. Such tumors are nearly always accompanied by effusion into the peritoneal cavity of material which is at first serous and later sanguineous. The symptoms are those of the primary disease supplemented by the presence of small or large masses intra-abdominally and the signs of ascites. The *prognosis* is, of course, practically hopeless, and *treatment* is only palliative.

Pseudomucinous cysts of the ovary often rupture and discharge the mucinous cells on to the peritoneal surface; they may also travel along the lymphatics of the mesentery and cause them to rupture. A chronic form of peritonitis results with growth of the cells into daughter tumors, and the formation of free fluid. The fluid is often mucinous in character. This disease is known as *pseudomyxoma peritonei*. It is relatively non-malignant, and, if not advanced, often retrogresses after removal of the mother cyst; in some instances, however, the disease follows a carcinomatous course.

Endotheliomata of the peritoneum have been described by Birch-Hirschfeld as arising primarily from the endothelial cells of the peritoneum and its lymphatics, particularly the latter. They appear in miliary form scattered extensively over the peritoneal surface. Cysts are sometimes present. As in other forms of peritoneal tumor, the irritation often causes ascites.

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ASCITES

Definition.—An accumulation of serous fluid in the peritoneal cavity.

Etiology.—Ascites may be referable to either general or local causes. Of the general causes, heart disease is the most common. Next in frequency come renal disease and cirrhosis of the liver. Of the local causes, chronic inflammation of the peritoneum, especially of the tuberculous type, is the most important. Abdominal tumors and metastatic neoplasms of the peritoneum may cause ascites, as may also obstruction in the portal circulation, such as hepatic cirrhosis, syphilis, aneurysm, and compression or obstruction of the inferior vena cava. More rarely ascites is seen in leukemia, pernicious anemia, and malaria.

Symptoms.—The abdomen is distended with fluid, which renders the percussion note dull, especially in the flanks. The dulness is movable and can be best demonstrated by having the patient lie first on one side and then on the other. When the effusion is large the abdomen becomes very tense and *lineæ albicantes* may be present. The superficial veins of the abdomen are often prominent and about the umbilicus a large group of distended veins may appear—the so-called *caput medusæ*. If a considerable amount of fluid is present, the heart and liver may be displaced upward. When the ascitic fluid is free, a distinct wave of fluctuation may be felt by placing the hand upon one side of the abdomen and tapping gently with the fingers of the other hand on the opposite side.

Diagnosis.—A large *ovarian cyst* may sometimes be confused with ascites. In the former condition the abdominal prominence is usually symmetrical, with little tendency to bulge in dependent parts, and there is lateral displacement of the uterus.

Ascitic Fluid.—The ascitic fluid is usually clear with a yellowish or greenish color and faintly alkaline reaction. The specific gravity varies from 1010 to 1015. It is distinctly albuminous and often coagulates on standing. In the ascites of cancer and tuberculosis it is often tinged with blood. When ascites is associated with jaundice the fluid may have a dark brown color. Centrifuging throws down a sediment composed of endothelial cells and usually a few leukocytes.

Treatment.—This, of necessity, is directed toward the cure of the underlying disease. Much may be accomplished by improving the functional activity of a damaged cardio-renal system. The amount of fluid in the diet must be limited.

In marked cases main reliance is placed upon the withdrawal of the ascitic fluid by a trocar (*paracentesis abdominalis*). This is accomplished by plunging the trocar and cannula through the anterior abdominal parietes and allowing the fluid to escape. Certain precautions are essential. The operator must be sure that no disease is present which might cause the bowel to be adherent to the abdominal wall. The point selected for the tap must be a dependent part. The bladder must be empty. Asepsis must be observed. Finally, the fluid must not be withdrawn too rapidly and provision must be made to replace the intra-abdominal tension by extra-abdominal pressure with a binder which is tightened as the fluid escapes. The safest and easiest site for inserting the trocar is half-way between the umbilicus and the symphysis pubis. The operation is performed with the patient in a sitting position. The use of a local anesthetic renders the introduction of the trocar painless.

Paracentesis may be repeated as often as necessary, but at subsequent tappings the possibility of a loop of intestine becoming adherent at the site of previous operations must be borne in mind.

Chylous Ascites.—Occasionally ascitic fluid has an opalescent milk-like appearance due to the presence of chyle. This chylous ascites is caused by a leak in the thoracic duct or one of its branches which results from obstruction or external violence. *Pseudochylous ascites* is very similar to the chylous form, but in the former the turbidity is due to the fatty degeneration of cells or to chemical substances of a non-fatty nature.

In both chylous and pseudochylous ascites the fluid is white or yellowish-white in color, but in the chylous form a layer of "cream" collects on standing, while in the pseudochylous form the creamy layer is usually absent.

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DISEASES OF THE RESPIRATORY SYSTEM

DISEASES OF THE NOSE

Under normal conditions air is warmed, moistened, and cleansed during its passage through the nose. The mucous membrane of the nose is continuous with that lining the accessory nasal sinuses and is everywhere rich in mucous glands. If the nasal passages are obstructed by deflection of the septum, by hypertrophy of the mucous membrane of the turbinates, or by enlarged adenoids, the mucous glands may be stimulated to increased activity and chronically produce a catarrhal discharge. This catarrhal process may, by spreading to the mucous membrane of the Eustachian tube, lead to changes in the middle ear that result in impairment of hearing. Obstruction of the nose favors pyogenic infection of the accessory nasal sinuses with such resulting symptoms as headache, chronic discharge of purulent material, much of which is swallowed, and the general disorders associated with focal infection.

Epistaxis is usually due to superficial ulceration of the anterior part of the septum. Hypertension, however, may cause rupture of the vessels in the posterior part of the nose and profuse hemorrhage. Hereditary multiple telangiectasis permits repeated hemorrhage that may lead to profound anemia. The telangiectatic areas in the nose and nasopharynx bleed more easily than those on the mucous membranes of the mouth or tongue. A blood-stained nasal discharge in a child always suggests enlargement and infection of the adenoids, nasal diphtheria, the presence of foreign body, or congenital syphilis; in adults it is frequently evidence of a new growth.

Infections of the Accessory Nasal Sinuses.—Etiology.—The most common cause of infection of the accessory nasal sinuses is *acute rhinitis*. *Abscesses* at the roots of the upper bicuspid and molar teeth often rupture into the maxillary sinus and produce infection which may give rise to no symptoms other than a chronic unilateral nasal discharge. A third cause of sinus infection is the entrance of *vomitus* into the sinus cavities during general anesthesia.

Symptoms.—The nasal communications of the accessory nasal sinuses are narrow and easily obstructed by the edema and discharge of thick mucus that accompany acute inflammation. This obstruction gives rise to headache, which is the most characteristic symptom of acute sinusitis. The mucous membrane of the nasal passages and accessory nasal sinuses is innervated by the trigeminus nerve, and the pain of sinus infection is most commonly referred to the area of distribution of this nerve. Infection of the sphenoidal sinuses, however, may give rise to suboccipital discomfort.

The headache or pain of sinus infection in contrast to that of hypertension, intracranial growths, neurasthenia, and eye strain is usually limited to the face. The pain of an acute infection of the frontal or maxillary sinus is usually localized over the affected sinus. Chronic infection, however, particularly of the maxillary sinuses, is often accompanied by discomfort over the forehead on the same side. Infection of an ethmoidal sinus usually causes discomfort in the orbit or across the bridge of the nose. Occasionally

the pain of a sinus infection is referred to the mastoid region, a fact explained by the innervation of the mucous membrane lining the mastoid cells by the trigeminus. In acute sinusitis the pain may be constant, but in the chronic condition it is characteristically more severe in the forenoon, and disappears toward evening.

Diagnosis.—Severe acute coryza or more general infection, such as influenza or pneumonia, is usually responsible for infection of an accessory nasal sinus. From 15 to 20 per cent. of all infections of the maxillary sinus are of dental origin. *x*-Ray shadows alone cannot differentiate between a sinus infection that is active and one that is clinically cured. The history, the presence of a discharge in the nose, the *x*-ray plate, and, when possible, irrigation of the suspected sinus, may all be necessary to establish diagnosis.

Treatment.—Sinus infections are local manifestations of infection of the respiratory tract. With the general therapy suitable for such an infection, the local application of heat and the use of astringents in the nasal passages usually relieve the acute symptoms. Nasal irrigations often cause aural infection and mastoiditis. If the pain of acute sinusitis is very severe, the patient should be referred to a rhinologist without delay, because this usually precedes the onset of complications. Chronic infections usually require special surgical treatment which favors better drainage.

Infections of the Accessory Nasal Sinuses in Children.—With the exception of the frontal sinuses, the accessory nasal sinuses are well developed at an early age. Children who are subject to recurrent respiratory infection often have foci in one or more nasal sinuses. Local treatment is rarely necessary. Removal of hypertrophied tonsils and adenoids usually relieves all the symptoms. A change of climate is beneficial.

Protein sensitization is a common cause of asthma in childhood, but the recognition and treatment of a sinus infection is an important part of the therapy of such conditions.

Complications of Sinus Infection.—*Retrobulbar neuritis* is perhaps the most frequent complication of sinus infection. It is characterized by impairment of central vision, particularly for colors, without evidence of choking of the disk or implication of the third, fourth, or sixth nerves. Inflammation or elevation of the optic disk, even when the posterior sinus is definitely infected, is usually due to syphilis or intracranial growth.

An *orbital abscess* is associated with unilateral exophthalmos; it is rare and must be differentiated from a new growth.

An *abscess of the frontal lobe* is the most frequent complication of chronic infection of the frontal sinus.

Tumors of the Nose and Nasopharynx.—New growths starting in the nasal passages are not infrequent in children. Fibroma and spindle-cell sarcoma are the common types. The *nasopharyngeal fibroma*, or "*juvenile polyp*," causes pressure necrosis of the bony structures and may invade the orbit or cranial cavity; it occurs only in males between the ages of ten and twenty-five years. On account of the great vascularity of these tumors radium therapy gives the best results.

In adults *sarcoma* is relatively rare in the nose, but is common in the nasopharynx. *Carcinomata* seldom cause obstruction because of early ulceration. Sarcoma gives rise to large tumors, and obstruction is one of the early symptoms of this type of growth.

Enlargement of the cervical glands may be the first sign of a naso-

pharyngeal growth, although obstruction to breathing, a blood-stained nasal discharge, or ringing in the ear, may be the initial symptom. Of 79 patients whose cases were reported from the Mayo Clinic, only 38 had nasal symptoms. Invasion of the pterygoid fossa with fixation of the jaw, pain, or anesthesia in the area of distribution of the second or third division of the trigeminus, invasion of the orbit with paralysis of certain of the extra-ocular muscles, or severe and constant headache from meningeal irritation are all common manifestations of malignant growth in the naso-pharynx.

Pyogenic infection of the accessory nasal sinuses is usually associated with all new growths arising in the nose. Similarly, infection of the ear commonly accompanies new growths arising in the nasopharynx.

The removal of a piece of growth for microscopic examination may be necessary to establish diagnosis, but encourages secondary infection which often leads to frequent and profuse hemorrhage.

Treatment.—On account of the anatomical relations complete surgical removal of a malignant growth is practically impossible, and irradiation is the most desirable therapeutic measure.

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DISEASES OF THE LARYNX

Stridor as a symptom may afford valuable clinical evidence as to the location of the lesion. *Inspiratory stridor* is particularly common in children and suggests laryngeal diphtheria, a foreign body, papilloma of the larynx, spasm, or inco-ordination of the muscles of the glottis –as in laryngismus stridulus. Almost any laryngeal irritation in a child may cause a glottic spasm, the most frequent manifestation being the crowing inspiratory stridor of catarrhal laryngitis (croup). *Expiratory stridor* suggests an obstructive lesion in the trachea or bronchial tree. This may be due to an inflammatory condition, as tracheal diphtheria, to asthma or pneumonia,

or to pressure from mediastinal tumors. Aneurysm is the most common cause of expiratory stridor in adults, while pressure due to tuberculous glands or an enlarged thymus is frequently provocative of this symptom in children. It is important to emphasize that no patient with a marked stridor should be submitted to general anesthesia. A patient with stridor is forced to use all his accessory respiratory muscles, and a general anesthetic is liable to make the respirations cease abruptly.

Early and frequent examinations of the larynx are important in the three following conditions: (1) Pulmonary tuberculosis predisposes to catarrhal changes in the larynx; tuberculous laryngitis is a common complication, and if recognized in its early stage absolute silence in association with general hygienic measures will usually bring about a cure. (2) The recurrent laryngeal nerves are in close approximation to the posterior capsule of the thyroid gland and may be injured by pressure exerted by an enlarged thyroid as well as by operative procedures on this gland. For this reason every patient with goiter should have a laryngeal examination both *before* and *after* operation. The prognosis of an operative lesion of the recurrent laryngeal nerve is favorable, provided the onset of the hoarseness is gradual and not immediate. (3) Hoarseness in a patient over forty that persists for more than three weeks is often due to cancer. If recognized early, the prognosis after operative removal and irradiation is good. If, however, examination is postponed until the appearance of evident clinical symptoms of malignancy, a cure rarely results from any method of treatment.

The Common Laryngeal Disorders of Children.—Catarrhal Laryngitis (*Croup*).—Certain children are peculiarly susceptible during the winter months to recurrent catarrhal laryngitis which is characterized by hoarseness, a harsh metallic cough, and inspiratory stridor. The attacks usually occur at night, and although often alarming are never fatal. In the morning the child is surprisingly well, and only a slight cough or hoarseness may persist. A similar attack may follow on the next night. When the attacks recur at frequent intervals it is advisable to search for a focus of infection or an obstruction in the upper respiratory tract.

Treatment.—The symptoms are the result of edema and glottic spasm. A hot bath, benzoin inhalations, wine of ipecac (1 drop for each two years of the child's age), and paregoric are the usual remedies. A laxative and rest in bed for a few days are desirable. Local applications to the nose and throat often increase the irritation. Menthol should never be used in young children because of its toxic effects. A few drops of albolene or a dilute solution (1 : 5000) of adrenalin in the nose temporarily relieve local congestion. After recovery an examination should be made for chronic infection of the accessory nasal sinuses, tonsils, or adenoids.

Diphtheritic Laryngitis.—The symptoms, diagnosis, and general treatment of diphtheritic laryngitis are discussed in the chapter on Diphtheria.

Intubation is necessary during the acute stage of the disease, but *tracheotomy* is rarely essential at this time unless simpler treatment fails to relieve the laryngeal obstruction. An attempt should always be made to remove the intubation tube on the fourth or fifth day. Both intubation and extubation must be performed gently and accurately. Trauma of the edematous and infected mucous membrane of the glottic and subglottic

region often leads to laryngeal stenosis due to the formation of scar tissue. In children under two years of age great care must be exercised in selecting the size of the intubation tube. Introduction of a four- or five-year tube into the larynx of a child twelve to eighteen months old may relieve obstruction, but often results in laryngeal stenosis that requires years of treatment. If a tube of the proper size is coughed out, there is a tendency to introduce larger and larger tubes. An oversized tube should always be removed at the end of twenty-four hours. If obstructive symptoms still persist and are not relieved by suction, it should again be introduced and left in place while low tracheotomy is performed under *local* anesthesia. Hasty operation; general anesthesia, which precipitates an arrest of the respiration; high tracheotomy, which encourages subglottic granulation; and the use of a cannula of improper size, shape, and material are common causes of laryngeal stenosis. When a blood-stained discharge is coughed out, it is wise to remove the tube permanently whenever possible.

Recently, intubation has been largely supplanted by the *removal of membranes* from the pharynx, larynx, and trachea with suction. This procedure is carried out under direct vision through an electrically lighted laryngoscope.

Chevalier Jackson states that five-sixths of all cases of chronic laryngeal stenosis that he has seen during the past thirty years have been due to faulty tracheotomy or improper after-care of the tracheal tube and wound.

Laryngismus Stridulus (*Laryngospasm*).—Laryngismus stridulus in children may be defined as a laryngeal stridor of sudden onset, without fever. It is rare during the first three months of life, and most common in children from six months to two years of age. Boys are more frequently affected than girls. It is uncommon in breast-fed infants and is nearly always associated with rickets. The laryngeal spasm is a manifestation of the extreme irritability of the nervous system in tetany.

Symptoms.—An attack is characterized by the sudden onset of inspiratory dyspnea without premonitory symptoms. Obstruction may be so marked as to cause temporary complete apnea with deepening cyanosis; unconsciousness, convulsions, or death may follow in severe cases. Usually, however, after fifteen or twenty seconds a characteristic deep inspiration shows that the glottic spasm has relaxed. There may be numerous subsequent attacks. The child may be normal between attacks or may show other evidences of tetany.

Diagnosis.—The age of the patient, the absence of fever, the periods of apnea followed by a characteristic crowing inspiration, and the associated clinical signs of tetany (carpopedal spasm, Chvostek's and Trousseau's signs, etc.) are pathognomonic. Since a foreign body lodged in the larynx may, however, produce almost identical symptoms, the larynx should be directly examined through a laryngoscope.

Treatment.—During the attack artificial respiration and cold applications to the face and chest are most effective. Intubation and tracheotomy are rarely necessary. Later the fundamental metabolic disturbances must be treated. Calcium chlorid (10–15 gr. every four hours for a child one year of age) and cod-liver oil (3j three times daily) should be administered for several weeks. In these cases woman's milk should, if possible, be obtained for infants less than eight months of age.

Foreign Bodies in the Larynx.—The sudden onset of paroxysms of

coughing and dyspnea in a healthy child suggests the presence of a foreign body in the larynx, trachea, or bronchi. Immediate tracheotomy may be necessary. Metallic bodies such as coins may be localized with the fluoroscope. Since less opaque bodies, such as fish bones, may not be demonstrable by the *x*-ray, direct examination of the larynx and trachea is necessary. In children all examinations should be conducted without anesthesia.

Papilloma of the larynx in children, though benign, has a mortality almost equal to that of carcinoma of the larynx in adults. Fortunately, it is relatively rare, only 20 cases having been seen at the Johns Hopkins Hospital from 1912 to 1924. It may appear at any age and is much more common in boys.

The exact *etiology* is uncertain, although recent experimental studies in Vienna suggest that an invisible, filtrable virus is the direct cause. Both in structure and behavior the lesion resembles that of verruca vulgaris of the skin. Even very slight trauma may cause implantation of new growths on the surrounding mucous membrane.

Symptoms.—The symptoms depend on the size and location of the tumor. Slowly developing but progressive hoarseness, a paroxysmal cough, and, at a later period, dyspnea, should excite suspicion of laryngeal growth.

Diagnosis.—Direct inspection of the larynx (without anesthesia) is necessary for positive diagnosis.

Treatment.—Simple removal of the tumor rarely results in cure, but, on the contrary, usually stimulates further growth. Repeated removal of the recurring growths and long-continued general hygienic measures are required to cure this condition. Early tracheotomy may be necessary. The results of radium and *x*-ray therapy are disappointing.

The Common Laryngeal Disorders of Adults.—Catarrhal Laryngitis.—*Acute catarrhal laryngitis* is usually secondary to infection of the upper respiratory tract, but may also be brought on by irritation from improper use of the voice, as well as by excessive use of alcohol or tobacco and by chemical fumes. The lesions in the larynx vary from slight subglottic hyperemia and edema to diffuse reddening of all the mucous membranes of the glottis and shallow ulceration. Hoarseness is the most constant symptom, but in the more acute condition there may be aphonia and a dry burning sensation in the throat. Catarrhal laryngitis is differentiated from tuberculous laryngitis by the absence of pulmonary symptoms; *true tuberculous laryngitis is always secondary to a pulmonary lesion.* The *treatment* consists in abstinence from speaking, cold applications, benzoin inhalations, regulation of the surroundings so that the air is moist and of even temperature, and rest.

Chronic catarrhal laryngitis is due to long-continued irritation from any of the causes of the acute condition. The pathological change which is usually most prominent in the posterior half of the larynx consists of thickening of the epithelium. This condition was originally described by Virchow as *pachydermia* and is not to be confused with carcinoma: the other lesions involve the vocal cords and the intrinsic muscles. In the larynx, as in the nose and nasopharynx, chronic irritation causes excessive secretion of thick, glairy mucus which produces many of the symptoms of chronic laryngitis. The cause of such chronic discharge from the upper air passages, especially pyorrhea, demands proper treatment. Baking the

larynx with hot air, much as a joint is baked, is perhaps the best local therapy. Any excessive growth of epithelium between the posterior ends of the cords should be removed.

Tuberculous laryngitis is always secondary to pulmonary disease. It is a common complication of pulmonary tuberculosis, its incidence varying from 15 per cent. in early tuberculosis to 70 per cent. in advanced conditions. In the earliest cases the symptoms and the appearance of the larynx are very similar to those typical of catarrhal laryngitis, but as the disease progresses the laryngeal lesion becomes characteristic. The early changes are usually localized in the posterior half of the larynx; those of the later stages consist in thickening or ulceration which are usually unilateral and therefore in contrast with those of catarrhal laryngitis. Pain on swallowing, often radiating to the ear on the same side, is a common symptom of tuberculous laryngitis and is due to ulceration in the larynx.

Treatment.—The larynx of patients with pulmonary tuberculosis should always be examined at frequent intervals. Hyperemia or swelling of the mucous membranes of the larynx should be treated as tuberculous laryngitis. The onset of hoarseness in an individual with pulmonary lesions demands immediate examination of the larynx and enforced silence.

The therapy is largely general and not local; absolute avoidance of speaking for six weeks or longer, removal of the patient from the city to a sanatorium in the country, exposure to sunlight, and adherence to the rules of general hygiene are necessary. The dysphagia may be relieved by injection of alcohol or surgical division of the superior laryngeal nerve. Ulcers should be cleansed with local applications of hydrogen peroxid, and granulations stimulated with the galvano-cautery. Tracheotomy must never be performed except for stenosis or suddenly developing edema.

Syphilitic Laryngitis.—The gumma, which is the common syphilitic lesion of the larynx, is usually situated above the vocal cords on one side. It is composed largely of dense, fibrous tissue, and, unless it ulcerates, produces no symptoms other than hoarseness and slight stridor. If ulceration takes place, the resulting scar tissue usually causes marked deformity and stenosis of the larynx. Laryngeal lesions associated with those of the mucous membrane of the pharynx in secondary syphilis may produce symptoms identical with those of acute catarrhal laryngitis. Acute laryngitis which does not respond to treatment within a reasonable time should arouse suspicion of syphilis. Simultaneous occurrence of both secondary and tertiary lesions in the throat is not uncommon.

Diagnosis.—The conditions to be differentiated are *tuberculosis* and *new growths*. The diagnosis depends largely on the evidence of syphilis elsewhere in the body, although it must be emphasized that tuberculosis and syphilis, as well as cancer and syphilis, are often associated.

Treatment.—Gumma of the larynx is very resistant to any general or local antisyphilitic therapy, and unless the local symptoms are urgent local laryngeal treatment is probably undesirable. Injury to a gumma, such as cauterization or excision of a piece for diagnosis, encourages secondary infection and ulceration. The secondary lesions in the throat and larynx are best treated intravenously.

Benign and Malignant Tumors of the Larynx.—*Benign Tumors.*—The most common of the benign tumors in the larynx are the polyp and the papilloma. The papilloma of the larynx in adults differs from that in

children in that it is usually solitary and shows far less tendency to recur after removal; furthermore, it is frequently of tuberculous or syphilitic origin. The symptoms of a laryngeal growth depend upon its location. The long, pedunculated polypi that grow on the vocal cords cause attacks of paroxysmal coughing and hoarseness due to interference with accurate approximation of the vocal cords. Benign growths seldom cause bleeding, pain, or dysphagia. They are best treated by local excision through the mouth, although local application of radium often causes complete disappearance of the more vascular type.

Malignant Tumors.—Carcinoma is almost the only malignant growth in the larynx; in the trachea and bronchi sarcoma is common. The point of origin of carcinoma is of considerable importance. If it arises on a vocal cord the tumor is usually situated on the anterior half. A tumor in this situation is termed "intrinsic" and is relatively benign. If the growth involves the mucous membrane over the arytenoid cartilages or the lateral walls of the larynx above the vocal cords, it is said to be an "extrinsic" growth, and the prognosis is bad. A carcinoma that arises from the posterior wall of the larynx, just above the opening of the esophagus, is the most malignant of all laryngeal growths.

Diagnosis.—It is of the utmost importance to recognize carcinoma of the larynx early, because only then can a cure be effected without recourse to radical, mutilating surgery. From 75 to 85 per cent. of carcinomata of the larynx develop in males between the ages of forty and sixty. The earliest symptom of a growth on a vocal cord is hoarseness; when this appears in an individual forty years old or more, it should be regarded as due to carcinoma until proved otherwise. As differentiation of a malignant from a benign growth is often difficult at this early stage, it may be necessary to remove a piece of tissue for microscopic examination. Extrinsic growths often ulcerate early, so that there may be bleeding, and pain on swallowing. The location of the earliest metastases of carcinoma of the larynx is in the deep cervical glands about the bifurcation of the common carotid artery.

Tuberculosis, syphilis, cancer, and *benign growths* may cause diagnostic confusion. The age of the patient, the appearance of the larynx, and the result of general physical examination must all be taken into consideration before arriving at a final diagnosis. Not infrequently a patient with cancer of the larynx is found to have a positive Wassermann reaction; in such cases there is danger of continuing antiluetic treatment until the growth has become inoperable. It is also not unusual to find both tuberculosis and carcinoma in a cervical gland removed for diagnosis.

Treatment.—Early removal of an *intrinsic carcinoma* and the affected cord results in a high percentage of cures. The *extrinsic growths* demand extensive surgery, and the results are far less favorable. Irradiation should follow every operation, but until we have had more experience with radium as a therapeutic agent, its use alone for early tumors that may be excised is unwise.

Laryngeal Neuropathies.—The muscles[1] that move the vocal cord are innervated by the recurrent laryngeal nerve, a branch of the vagus. This is frequently involved in pathological processes and hoarseness results. The common cause of a *recurrent nerve palsy* is an aneurysm of the arch of the aorta. Other causes are a mediastinal growth, tuberculosis of the apex

[1] The cricothyroid, a tensor muscle, is supplied by the superior laryngeal nerve.

of the right lung implicating the pleura, dilatation of the left auricle, as in mitral stenosis, carcinoma of the esophagus, carcinoma and occasionally hypertrophy of the thyroid, and metastasis and inflammation of the glands in the neck that involve the vagus. Postdiphtheritic and syphilitic neuritis may also cause laryngeal palsies. There are, too, so-called *functional laryngeal palsies*, which may be distinguished from the organic type by the sudden onset of complete aphonia without loss of ability to cough and laugh, and by the movements of the vocal cords revealed by the laryngeal mirror.

The recurrent nerve lies close to the posterior capsule of the thyroid gland, and the onset of hoarseness following thyroidectomy indicates that it has been injured. If the nerve is divided, hoarseness ensues immediately and may never entirely disappear. If the hoarseness comes on gradually, however, it may be due to stretching or edema of the nerve, and the voice will ultimately return to normal. If during operation both nerves are injured but not divided, inspiratory stridor develops suddenly because of inability of the cords to open during inspiration. Temporary tracheotomy may be necessary.

The *prognosis* for complete restoration of function following postdiphtheritic paralysis is good. The laryngeal crises of tabes are really glottic spasms depending on syphilitic neuritis of the recurrent nerves. For this condition also tracheotomy may become necessary, since antiluetic therapy is not always effective.

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Diseases of the Bronchi

BRONCHITIS

The term "tracheobronchitis" is usually more accurate than "bronchitis," since tracheitis often precedes or is associated with ordinary bronchitis. The involvement may, however, be confined to the smaller bronchial tubes, in which case tracheal involvement is slight or absent. The term "capillary bronchitis" implies an involvement of the finer bronchi and bronchioles, a condition which rarely, if ever, occurs except during bronchopneumonia. Clinically at least the causes, symptoms, and treatment of capillary bronchitis and bronchopneumonia are the same.

The careful physician is seldom satisfied with a diagnosis of simple bronchitis, since not infrequently the acute form and almost always the chronic form are secondary to or associated with other more important lesions. Unless search is made for these they may be overlooked or overshadowed by the symptoms and signs of bronchitis. In prevention, diagnosis, and treatment this broad concept of what is considered a common and simple malady is of first importance.

Acute Bronchitis (*Acute Catarrhal Tracheobronchitis*).—Etiology.—*Microbic invasion* is the usual cause of acute bronchitis. There is no specific causative organism, the *Streptococcus, Pneumococcus,* and *Bacillus influenzæ* being the most common invaders. In many cases the infection is polymicrobic. Not infrequently acute bronchitis results from extension of ordinary coryza or laryngitis; and it may constitute part of the clinical syndrome of such acute infectious diseases as measles, whooping-cough, influenza, typhoid fever, etc. In the tropics, a specific type of bronchitis is associated with spirochetal infection (see Spirochetal Bronchitis). There are several *predisposing factors,* the most important of which are perhaps sudden variations in temperature and barometric pressure. Rickets in infancy, disease of the tonsils and adenoids in children of pre-school and school age, and nutritional disturbances in the adult all play a rôle. The disease may develop in individuals of any age, but is most common and serious at the extremes of life.

Chemical and Mechanical Causes.—Tracheobronchitis may follow the inhalation of irritant vapors (ammonia, chlorin, bromin, etc.) accidentally, in certain occupations, or during warfare. The irritating dust particles that are inhaled in many of the dusty trades and the lodgment of foreign bodies in the trachea or bronchi may produce acute bronchitis (see Arachidic Bronchitis).

Morbid Anatomy.—The changes in the mucous membrane consist of an initial dryness characterized by hyperemia and swelling, with diminution of the bronchial secretion. The epithelium is swollen and desquamates, and the submucosa becomes infiltrated with exudate. This condition is followed by an excessive production of mucus by the bronchial glands and the appearance of the exudate on the surface. The expectoration at this stage is largely mucoid, but later and in severe cases the products of inflammation may give it a mucopurulent or purulent character. Ordinarily the inflammation subsides without complications or sequelæ, and the mucosa returns to normal. Less often the lesion becomes chronic; bronchial dilatation may occur; or, by extension downward, the condition may develop into bronchopneumonia.

Symptoms.—The *cough* is an early and constant symptom. At first it is frequent, dry, distressing, and accompanied by substernal soreness or "tightness in the chest." Later it raises sputum which is at first scanty and mucoid, then abundant, and mucoid or mucopurulent in character. There may be slight or no constitutional disturbance. Not infrequently the *onset* is characterized by chilliness, slight fever, headache, malaise, and pains in the back and extremities. In the more *severe form*, which is apt to develop during infancy and old age and in debilitated patients, high fever and marked constitutional disturbance may occur. *Herpes* is not uncommon in the acute bronchitis due to pneumococcus infection. Ordinarily, in the course of several days, the cough loosens, expectoration becomes free, the soreness in the chest disappears, and the constitutional symptoms abate. Recovery may, however, be delayed for several weeks.

Physical Signs.—Mild bronchitis of the larger tubes may produce no signs of abnormality. Palpation may elicit *rhonchal fremitus* over one or both lungs, especially during active inspiration. The percussion note is not altered. Auscultation reveals normal, enfeebled, or harsh vesicular breath sounds depending upon the degree of interference with the air currents. In the early dry stage, coarse sonorous and sibilant râles are audible during inspiration and expiration. Their appearance and disappearance is varied by coughing and forcible breathing. In the later stages, as secretion accumulates, the râles become bubbling in character.

Diagnosis.—The history of a recent cough with substernal soreness and the presence of distinctive physical signs usually renders the diagnosis fairly easy. The more severe types, with sudden onset, fever, and constitutional symptoms, may suggest *lobar pneumonia*. The absence of dyspnea, cyanosis, and lobar consolidation point to bronchitis. *Bronchopneumonia* without distinctive signs may also simulate acute bronchitis. The differentiation depends upon the findings outside of the chest—dyspnea, cyanosis, and high fever being distinctive features of bronchopneumonia. The acute bronchitis associated with the specific infectious diseases may precede the development of the clinical features characteristic of these diseases, and differentiation from *simple bronchitis* is impossible until after the appearance of Koplik's spots, exanthem, whoop, etc.

The possibility of *pulmonary tuberculosis* should be kept in mind, since this disease is ushered in at times by evidences of acute bronchitis. The sputum should always be examined for *tubercle bacilli*, the apices carefully examined, and inquiry made as to possible contact with tuberculosis, antecedent pleurisy, hemoptysis, or gradual loss of weight and strength. The likelihood of tuberculosis is strengthened when the bronchitis persists for more than four weeks; when the signs of bronchitis are localized at the top of the lung; when the expectoration is streaked with blood; and when an afternoon elevation of temperature continues and there is loss of weight and strength.

Prognosis.—The prognosis varies with the previous health of the patient and the severity of the attack. In most adults acute bronchitis is benign. At the extremes of life and in debilitated individuals it often progresses into bronchopneumonia, with its attendant high mortality.

Treatment.—Rest in bed is the most valuable measure for hastening recovery from acute bronchitis. This should be continued until the temperature is normal and the constitutional symptoms have disappeared.

If the patient is seen early in the attack a hot foot bath, a glass of hot lemonade, and rest in bed between blankets will induce a profuse perspiration which is helpful in relieving the bronchial congestion. Dover's powder likewise induces perspiration and is valuable in allaying cough. The soreness or "tightness" in the chest is relieved by mustard plaster. An initial purge and the free ingestion of water are desirable. Codein may be given in $\frac{1}{4}$-grain doses as often as necessary to allay the excessive, dry, and harassing cough of the early stages. The so-called sedative expectorant combinations, which contain ipecacuanha, potassium citrate, and opium in some form, have been much abused. They tend to upset the stomach and are not more effective than codein. In children, an initial dose of castor oil and a "fever mixture" consisting of tincture of aconite, spiritus etheris nitrosi, and liquor potassii citratis, have been found empirically to be of service in the early stages to allay irritability. The use of medicated vapors or moistening of the air by steam are seldom necessary except when there is considerable dry cough with soreness in the chest and such evidence of laryngeal irritation as hoarseness and brassy cough. The compound tincture of benzoin to which a small quantity of eucalyptol and spiritus camphoræ have been added may be heated in water (2 drams to a quart) and allowed to vaporize slowly in the room.

In the later stages the so-called stimulating expectorants should be administered, the most important of which is ammonium chlorid (gr. 5 or 10 every third hour). If the patient coughs more than is necessary to raise the sputum small doses of codein may be added to the ammonium chlorid. Some simple combinations are as follows:

℞. Ammonii chloridi ..... ʒvj
Codeinæ sulphas ..... gr. viij
Syrupi acidi citrici ..... fʒiij
Aquæ destillatæ ..... q. s. ad. fʒvj.—M.
Sig.—One teaspoonful in $\frac{1}{4}$ glass water every three hours.

℞. Ammonii chloridi ..... fʒiv
Mistura glycyrrhizæ comp. ..... fʒiv.—M.
Sig.—One teaspoonful in $\frac{1}{4}$ glass water every three hours.

℞. Elixir terpin. hydrat. et codein ..... fʒiv.—M.
Sig.—One teaspoonful in $\frac{1}{4}$ glass water every four hours.

In the terminal stages, when the cough is clearing but the expectoration persists, oleum santali (minims 5 to 10 every four hours) is useful, but as it is apt to disturb the stomach and irritate the kidneys it must be administered with care. During convalescence iron and arsenic, tonics, cod-liver oil, and in the summer a sojourn at the seashore or in the country, hasten recovery.

The prevention of bronchitis and its recurrence involves a consideration of the etiological factors.

Chronic Bronchitis (*Chronic Catarrhal Tracheobronchitis*).—ETIOLOGY.—Chronic bronchitis may follow repeated exposure to the causes of the acute form. The constant inhalation of dust in certain occupations, such as mining, polishing, grinding, stone cutting, pottery making, dealing with cement, milling, etc., is one of the commonest causes of chronic bronchitis. Usually chronic bronchitis is a secondary disease associated with the pulmonary changes of emphysema, interstitial pneumonia, pneumoconiosis, and tuberculosis, and in varying degrees of severity with the chronic pul-

monary congestion of cardiovascular disease, especially mitral lesions. Aneurysm of the aorta and enlarged tracheobronchial glands may cause an intractable bronchial inflammation by pressure. Chronic bronchitis usually occurs in adults and is common in elderly people during the winter with a tendency after a while to persist throughout the year. Gout, syphilis, alcoholism, excessive smoking, and debilitating diseases predispose to chronic bronchitis. The exciting bacteria are similar to those which are found in acute bronchitis.

Morbid Anatomy.—In certain cases the bronchial mucosa shows a variable degree of redness and swelling with epithelial denudation. There is leukocytic infiltration of the mucosa and submucosa with fibrous-tissue formation, which tends to extend through the bronchial wall and thus lead to chronic peribronchitis. The surface of the membrane is covered with an excessive secretion of mucus and an inflammatory exudate. The expectoration consequently is mucoid or mucopurulent in character. In other instances the mucosa is pale and atrophic; the bronchial secretion and morbid exudation scanty or absent.

Emphysema is a frequent complication, and bronchiectasis is not an uncommon result of chronic bronchitis. Hypertrophy and dilatation of the right heart may result from the increased pressure in the pulmonary circulation.

Symptoms.—*Simple chronic bronchitis* is characterized by a *chronic cough* and *expectoration*, both of which vary in severity from time to time. The cough, which is frequently periodic or paroxysmal, is relieved by the expectoration of varying amounts of mucoid or mucopurulent material. The cough and expectoration are most marked early in the morning, but several paroxysms may occur during the day. The *"winter cough"* of old people is a manifestation of the simple chronic bronchitis which undergoes acute exacerbations during the winter months. When emphysema is associated with bronchitis *dyspnea* on exertion is common. *Constitutional symptoms* are usually absent.

Several clinical variations of the condition have been described: (*a*) *Chronic dry bronchitis* or the *catarrhe sec* of Laennec, which is characterized by severe paroxysms of coughing with expectoration of little or no tenacious sputum. This type is not uncommon in old people with emphysema. (*b*) *Bronchorrhea serosa* or the *catarrhe pituiteux* of Laennec which is characterized by an abundant, thin, frothy, odorless sputum containing but few cells. (*c*) *Putrid bronchitis*, in which the expectoration is mucopurulent and *offensive* in odor, and which is almost invariably associated with bronchiectasis, abscess, gangrene, perforative empyema, or some lesion involving changes in the lung. Simple chronic bronchitis, *per se*, probably never causes the formation of fetid expectoration. (*d*) *Eosinophile bronchitis* of Tiechmüller, which is characterized by the expectoration of a mucoid substance containing an abundance of eosinophilic cells and by an increase in the number of such cells in the blood. It is probably related to asthma.

Chronic secondary bronchitis is a term which refers to that large group of disturbances in which the bronchitis is secondary to pulmonary, cardiovascular, or renal disease. The bronchitis *per se* does not differ essentially from the simple chronic type except that the sputum is more likely to be tinged with blood and that frank hemoptysis is not uncommon. Dyspnea may be an early symptom, especially during cardiovascular disease. Chronic

bronchitis persists for years with clinical features which vary with the associated pathological conditions, the development of complications, such as emphysema and bronchiectasis, and the right cardiac hypertrophy and dilatation which eventually supervene with pulmonary congestion, enlargement of the liver, ascites, and edema of the extremities.

Physical Signs.—The physical signs resemble those of acute bronchitis, but are modified by coexisting emphysema, tuberculosis, pneumonoconiosis, heart disease, etc. The signs of long-standing simple chronic bronchitis are mainly those of the associated emphysema. Dyspnea and cyanosis are present. The chest is rounded; respiratory movements are restricted; vocal fremitus is enfeebled; percussion tends to hyperresonance; auscultation reveals feeble breath sounds, with prolongation of expiration, and numerous coarse râles of a sonorous, sibilant, or bubbling character. In some instances râles may be absent.

Diagnosis.—Simple chronic bronchitis must be distinguished from that secondary to some organic disease, such as tuberculosis, the irritation produced by a foreign body, pneumoconiosis, and cardiovascular or renal disease; it must also be determined whether it is associated with emphysema or bronchiectasis. A careful history, a complete physical examination, sputum and Roentgen-ray studies should reveal sufficient evidence for easy differentiation. *Emphysema* is associated with distinctive signs which have been mentioned. *Bronchiectasis* should be suspected when, in addition to the periodic cough, there is expectoration of a copious and foul-smelling sputum which separates into layers in a conical receptacle. Signs of pulmonary contraction and clubbing of the fingers should confirm this suspicion. The *x*-ray is invaluable for differential diagnosis.

Treatment.—The treatment of simple chronic bronchitis consists in removal of the causative factors which continue to exert an undesirable effect both locally and generally. Recurrent respiratory infections should be prevented, foci of infection in the upper respiratory tract removed, the occupation changed if dust is the noxious influence, and the smoking of tobacco stopped. The general condition of the patient should be improved by fresh air, sunlight, nutritious food, and abundant rest. Elderly patients who have "winter coughs," and those who are debilitated, obtain striking benefit from a change to a warm equable climate. For the *dry catarrh*, a sojourn at the seashore, *e. g.*, along the Jersey coast in summer, or in Florida in winter, has proved most helpful.

The *medicinal treatment* of chronic bronchitis is largely symptomatic. A warm saline gargle in the morning often facilitates expectoration. If the cough is excessive and apparently out of proportion to the degree of expectoration, small doses of codein (gr. $\frac{1}{4}$) or sodium bromid (gr. 15–20) may be given and repeated. Expectorants are much abused. They should be given with care, since they frequently upset digestion. Creosote, ammonium chlorid, terpin hydrate, squills, and senega, are frequently advocated, but are seldom necessary. Syrup of hydriodic acid may have a very favorable effect in simple chronic bronchitis. In the elderly and in the debilitated who have difficulty in removing the abundant expectoration, strychnin (gr. 1/30–1/20 every four hours) is of service.

The treatment of the acute exacerbations of chronic bronchitis is that of acute bronchitis. *Vaccines* may be helpful in protecting against recurrent infections, and occasionally in reducing the amount and offensive

character of the sputum. Since chronic bronchitis is but rarely an independent disorder, treatment must be directed toward the primary condition, rest and digitalis for myocardial insufficiency, rest and hygienic care for tuberculosis, elimination in renal disease, etc. The chronic bronchitis secondary to the lodgment of a foreign body in the bronchi disappears promptly after bronchoscopic removal.

Bronchitis obliterans is an unusual form of bronchitis characterized by an ingrowth of connective tissue which partly or wholly occludes the lumen of the terminal bronchi or bronchioles. It was first described anatomically by Lange in 1901 and was shortly thereafter recognized in a living patient by Fränkel. The inhalation of the fumes of nitrous acid, lime, and chlorin; phosphorus poisoning; measles; diphtheria; pertussis; the trauma caused by a foreign body; and lobar pneumonia have been considered as *etiological factors*. Except when associated with pneumonia the lesions are *diffuse*. The lung on section presents numerous grayish-white nodules similar to miliary tubercles, but easily differentiated under the hand lens by their angular or stellate form and their connection with the bronchioles. Microscopically the nodule is composed of a bronchiole partly or completely obliterated by connective tissue. The pulmonary tissue shows relatively little change except emphysema. The *symptoms* at the onset are those of severe acute bronchitis: they subside for a varying interval and then recur with dyspnea and cyanosis. The *physical signs* at this time are those of bronchitis with acute emphysema. Coarse and generalized crackling râles can be heard throughout the chest. In Fränkel's case the symptoms developed sixteen days after the inhalation of irritating fumes, and death ensued three days later. In Eden's case the symptoms developed after ten days, and death took place on the twenty-sixth day. Some patients have recovered, but the *prognosis* is grave. The *treatment* is symptomatic.

Spirochetal bronchitis is common in tropical countries, and is characterized by the presence in the sputum of *Spirocheta bronchialis*. The disease, which was discovered by Castellani in 1905, has been found in Ceylon, the West Indies, the Philippine Islands, and Africa. Recent reports indicate that it occurs in Europe and the United States. It assumes acute, subacute, and chronic forms. The *symptoms* of the *acute form* resemble those of acute bronchitis—fever, cough, and expectoration. In the *subacute form* there is little or no constitutional disturbance; the cough and expectoration exist alone for a few weeks. The *chronic form* follows the acute attack in some instances, but more frequently is insidious in onset. The cough, expectoration, hemoptysis, absence of fever, or hectic fever, and the loss of weight and strength constitute a clinical picture like that of tuberculosis. In all forms hemoptyses are common. *Physical examination* reveals signs not unlike those of ordinary bronchitis. When the pulmonary parenchyma is involved (bronchopulmonary spirochetosis) signs of localized consolidation may be obtained. The *diagnosis* depends upon the finding of *Spirocheta bronchialis* in the sputum. The presence of this organism and the absence of the *tubercle bacillus* differentiate the condition from *tuberculosis;* and the absence of characteristic ova distinguishes it from *paragonimiasis*. The *prognosis* is good when patients are *treated* promptly by rest in bed, hygienic-dietetic care, and the administration of arsenic in the form of Fowler's solution or neo-arsphenamin. The iodids have been of service.

Fibrinous Bronchitis (*Plastic, Croupous,* or *Pseudomembranous Bronchitis*).—Fibrinous bronchitis is a rare disease of unknown etiology. It is characterized by the formation in the bronchi and smaller bronchial tubes of branching casts which are expectorated by the patient during a paroxysm of coughing. It should not be confused with the acute fibrinous bronchitis which at times accompanies laryngeal diphtheria and is due to the diphtheria bacillus. The condition must also be distinguished from those in which the development of branching casts is a secondary and occasional feature, as, for example, in croupous pneumonia, tuberculosis, chronic heart disease, scarlet fever and measles. Branching casts are sometimes found in the albuminous expectoration which in rare instances follows paracentesis for pleural effusion.

Etiology.—The cause of this rare disease is unknown. Less than 100 cases have been reported. A variety of bacteria have been found, but no specific organism has been identified. The disease is more common in middle life, and attacks men more often than women. Some observers believe it to be analogous to *mucomembranous colitis* and *mucomembranous dysmenorrhea.* Experimental work seems to indicate that during an excessive secretion of mucin a precipitating ferment called *mucinase* is secreted; and that this can be identified in the serum of patients suffering from mucomembranous disturbances, whether they are located in the bronchi, intestines, or uterus. These facts, however, still require confirmation.

Morbid Anatomy.—The changes in the mucous membrane are not unlike those of ordinary bronchitis. The mucous glands show evidence of excessive activity. The most striking abnormalities are the casts or molds of the bronchi and smaller branchioles, which are branching in character, tubular or solid, and composed in greater part of mucus and fibrin. A section of the larger branches of the cast reveals a concentric lamination which indicates that the material is deposited in layers, the innermost ring being the oldest. The usual microscopical picture is that of a fibrillar stratified substance with epithelial cells, leukocytes, and bacteria in its meshes. Charcot-Leyden crystals and Curschmann spirals may be present. The small irregularities on the surface of the casts which are often noticed are supposed to be produced by air bubbles.

Symptoms.—The symptoms of the *acute* form are at the onset those of moderately severe acute bronchitis with chilliness, fever, and a cough which becomes paroxysmal and is associated with attacks of urgent dyspnea. There is a feeling of tightness and oppression in the chest. After some hours relief is obtained when the cast is expectorated. Hemoptysis may occur, but is uncommon. Fragments of casts may be coughed up before the larger pieces appear. After the cast has been expectorated the patient may recover entirely or may feel better for a few days until the formation of another cast induces a second attack of distressing cough and dyspnea. The number of casts expectorated during an attack is remarkably few. There may be only one.

The symptoms of the *chronic* form are those of chronic bronchitis with periodically recurrent attacks not unlike those of the acute form, but less severe. Fever may be slight or absent. The paroxysms of coughing and dyspnea are relieved when the casts are expectorated. This chronic type usually persists for years with recurrent attacks at varying intervals, weeks, months, or years.

Physical Signs.—The physical signs may be not unlike those of ordinary bronchitis; indeed, in many cases, it is impossible to elicit distinctive signs. Dyspnea and cyanosis are obvious during an acute attack. When bronchial obstruction occurs there is localized limitation of motion, decreased vocal fremitus and vocal resonance, normal or impaired percussion resonance, and enfeeblement of the breath sounds. Apart from the râles which are similar to those heard in bronchitis, there is at times a curious adventitious sound caused by the flapping to and fro in the air currents of detached portions of the casts. This dry, coarse, clicking sound the French call *bruit de drapeau*.

Diagnosis.—The diagnosis depends upon the presence in the sputum of the branching casts. These may be overlooked if the sputum is not carefully examined, since when expectorated they are usually coiled in rounded pearl gray or whitish masses covered with mucus. When these ball-like masses or coils are floated on water and unraveled their branching character is revealed. If the casts come from the *upper* bronchial tree they rapidly divide into short branches; if from the *lower*, the branches are longer.

A careful history, the association of other clinical features, the sputum examination, *x*-ray study, and in suitable cases bronchoscopy, should facilitate differentiation from aneurysm, asthma, the effects of a foreign body, tumor, etc. Special care is necessary in distinguishing *primary fibrinous bronchitis* from those conditions in which the formation of casts is secondary; such as tuberculosis, pneumonia, and heart disease. No difficulty will be encountered if the associated clinical features are kept in mind.

Prognosis.—In severe acute attacks dislodgment of the cast with consequent occlusion of the main bronchus or impaction in the larynx may cause immediate death. In the mild acute form of the disease the tendency is to recover. In the chronic forms the mildness of the attacks usually permits a favorable prognosis, but the predisposition to emphysema curtails the duration of life.

Treatment.—There is no known remedy which will satisfactorily hasten the removal or prevent the formation of casts except perhaps *potassium iodid*. This is recommended by most physicians. During an acute attack application of a mustard plaster to the chest and moistening the air of the room help relieve the oppression in the chest. Alkaline sprays (lime-water) are thought by some to be of value in softening and separating casts. With the development of bronchoscopy a more satisfactory treatment will probably be evolved. *Bronchoscopy* may be a life-saving procedure if suffocation is imminent because of dislodgment of the cast and occlusion of the main bronchus. *Tracheotomy* may be necessary in case of laryngeal impaction. In the intervals between the attacks of the chronic disease the treatment is that of chronic bronchitis.

Elmer H. Funk.

BRONCHIECTASIS

Definition.—A term applied to a condition characterized by cylindrical, fusiform, or sacculated dilatation of the bronchi. It is of two types

—congenital and acquired. *Congenital bronchiectasis* is a rare condition which is of interest chiefly to the pathologist. Two forms have been described: (*a*) *Fetal bronchiectasis*, a congenital cystic disease, in which a large bronchus and its branches show secondary and tertiary dilatations or cyst-like formations in the walls. There may be a large central cyst with which the smaller cysts communicate. (*b*) *Atelectatic bronchiectasis*, in which the bronchi become gradually widened as a result of developmental defect or collapse of the pulmonary parenchyma shortly after birth. *Acquired* bronchiectasis is of more importance clinically and is discussed in the following paragraphs.

Etiology.—Bronchiectasis is a secondary condition produced by a wide variety of lesions which involve the bronchi, lung parenchyma, and pleura. Three factors are operative in the production of the dilatation: (1) a lesion leading to softening of the bronchial wall, (2) a distending force, and (3) traction on the wall from without. Dilatations are prone to occur, therefore, whenever the integrity of the bronchial wall is impaired, as, for instance, during acute and chronic inflammations; when, in addition, there is an increase in the intrabronchial pressure as a result of bronchial obstruction; or when the lumen is narrowed by pressure from without, as in aneurysm, enlargement of the glands, tumor, etc. The distending force is usually expiratory and associated with explosive cough. The weight of accumulated secretions beyond an obstruction may be an etiological factor. Bronchiectasis may occur in pulmonary fibrosis, especially when there are pleural adhesions, as a result of traction on the bronchial walls. An acute bronchiectasis was not infrequently found at necropsy during the influenza epidemic of 1918 and 1919. Since the influenza bacillus is commonly associated with chronic bronchiectasis, it has been suggested that it may have its origin in a mild acute bronchiectasis which is at first unrecognizable, but becomes evident with the lapse of time.

Pathology.—Bronchiectasis may be acute or chronic. In the *acute form* seen during the influenza epidemic, the lung, in extreme cases, had a honeycombed appearance. The *chronic form* is more common. In this the bronchiectatic dilatation, which may be cylindrical, fusiform, or saccular in character, involves the whole or part of the lung. The sacculated dilatations are usually the largest. In more than half the cases the lesion is unilateral and the bases are more frequently involved than the apices. The bronchiectasis associated with tuberculosis most frequently affects the upper lobes, while the non-tuberculous form characteristically involves the lower portions of the lungs. The bronchiectatic cavity is differentiated from that due to tuberculosis by the smooth walls lined with epithelium and the remnants of bronchial structure in the wall. The points of entrance and exit of the bronchi may be seen. The cavity contains a secretion which is rendered fetid by the activity of putrefactive bacteria. The wall of the bronchiectatic cavity may become ulcerated and the lung tissue exposed. Fibrosis, abscesses, or gangrene may be found in the lung parenchyma. As a result of the increased resistance in the pulmonary circulation, hypertrophy and dilatation of the right heart occur and, eventually, the lesions of congestive heart failure. At necropsy lardaceous disease, suppurative pleuritis, pericarditis, and intracranial abscess may be found.

Symptoms.—The onset is usually insidious and masked by the symptoms of the primary condition. When fully developed the symptoms are

distinctive. The *cough* occurs in paroxysms, and an early morning attack is almost invariable. This may be repeated once or several times during the day. The paroxysms are associated with expectoration of large amounts of fetid sputum. In some instances mouthfuls of such material may be expectorated at one time. In the intervals between paroxysms the cough and expectoration are usually slight or absent for hours. The *sputum* separates, on standing, into three layers: the upper layer frothy; the intermediate, composed of thin, turbid, greenish fluid; and the lower, a heavy sediment of pus, cellular débris, bacteria, fatty acids, and hematoiden crystals. Small yellowish-brown masses called *Dittrich's* or *Traube's plugs*, and, if erosion of the bronchial wall has occurred, elastic fibers, may be found in the sediment. Not infrequently the sputum is blood tinged, and hemorrhages may occur from time to time. *Dyspnea* on exertion is common. *Constitutional symptoms* are absent as long as there is free evacuation of the offensive secretions. The general health remains fairly good. When free drainage is interfered with the sputum becomes scanty, the cough more frequent, and the paroxysms more severe. There is fever, malaise, pallor, and loss of weight and strength in varying degrees. These same symptoms develop when an acute bronchitis is superimposed upon the bronchiectasis. It must not be assumed that the paroxysmal cough and abundant fetid expectoration are invariably associated with bronchiectasis. The writer has seen a group of patients with involvement of the upper lobe without paroxysmal cough and fetid expectoration. The *clubbing of the fingers* which is ordinarily quite constant was likewise frequently slight or absent. Such conditions are usually seen in patients with healed or healing tuberculosis of the upper lobes. The apical character of the bronchiectasis allows freer drainage, and the secretions do not become stagnant as when the lower lobes are involved.

Physical Signs.—The patient not infrequently appears to be in good health. The skin, however, usually takes on a pale, slightly cyanosed tinge which, although difficult to describe, is readily recognized as evidence of disease. Dyspnea and rapid pulse occur on exertion. In very mild cases the physical signs in the chest are those of chronic bronchitis. Not infrequently they are masked by those of the associated lesion, fibroid tuberculosis, interstitial pneumonia, tumor, etc. In a typical case there is flattening and restriction of motion on the affected side. The distinctive signs are those of cavity formation—increased vocal fremitus, a high-pitched tympanitic note (perhaps a cracked pot sound), bronchophony or whispering pectoriloquy, cavernous or amphoric breath sounds, and medium and coarse bubbling râles. If the bronchiectatic dilatations are filled with secretion, dulness and distant breath sounds may be heard. The signs before and after a paroxysm of cough and expectoration may vary greatly. The signs of bronchiectasis are mixed with those of the coexisting bronchitis, emphysema, and fibrosis. In marked pulmonary fibrosis the heart may be drawn toward the affected side. Apart from this, there is usually some enlargement of the right heart and in the terminal stages evidence of heart failure. A very characteristic sign to be seen in nearly all cases is incurvation of the finger-nails and a bulbous enlargement of the terminal phalanges, to which is applied the term "clubbed fingers." The root of the nail is loosened from its periosteal attachment and the skin about the nail root becomes tense and glossy. The fingers alone may undergo these changes or the long

bones may also be involved (hypertrophic pulmonary osteo-arthropathy of Marie).

Complications.—Septic pericarditis and pleuritis, pulmonary abscess and gangrene, bronchopneumonia, cerebral abscess, and lardaceous disease are occasionally seen as complications of bronchiectasis.

Diagnosis.—A history of a chronic paroxysmal cough, with expectoration of considerable quantities of foul-smelling sputum, is suggestive of bronchiectasis. Distinct clubbing of the fingers should also bring this disease to mind, since it is most commonly associated with this condition. Apical bronchiectasis frequently accompanies *tuberculosis;* when apical and non-tuberculous it can be differentiated from tuberculosis only by examination of the sputum. Basal bronchiectasis with clear apices is usually non-tuberculous. The history, physical signs, findings in the sputum, and *x*-ray studies are necessary for differentiation of the underlying conditions which give rise to bronchiectasis (pneumoconiosis, tuberculosis, foreign body, tumor, etc.).

The expectoration is fetid in gangrene, perforative empyema, and abscess of the lung as well as in bronchiectasis. In *acute abscess* and *gangrene* the constitutional symptoms are marked. The sputum in gangrene is extremely fetid. The differentiation of bronchiectasis from chronic abscess is at times impossible, and the two lesions may occur together. An *empyema* which has perforated the bronchus is often associated with the sudden expectoration of abundant quantities of foul, purulent material. A history of an acute illness and the signs of pleural involvement can usually be obtained in perforative empyema. The bronchoscope in skilled hands is a great aid in differentiating the lesions simulating and producing bronchiectasis.

Treatment is directed toward diminishing the amount of expectoration and improving the patient's general condition. Rest, fresh air, and nourishment are of first importance. Certain *postures* facilitate drainage. Hanging the head over the edge of the bed until it touches the floor, bending over a chair, stooping forward, or elevating the foot of the bed often expedite the emptying of the bronchiectatic cavities. *Bronchoscopic drainage*, when skilfully performed, is the best method of insuring complete evacuation of the accumulated secretions. This procedure may be repeated at weekly intervals. Bronchoscopy permits the direct application of whatever medical substances may be necessary. *Surgical treatment* has been attempted, but the results are not particularly encouraging. The medicinal treatment is that of chronic bronchitis.

Acute Bronchiolectasis.—Carr in 1891 called attention to the occurrence of acute bronchiolectasis in badly nourished, syphilitic, or rachitic children with acute bronchitis, measles, pertussis, etc. These children are prone to develop not only bronchopneumonia but also dilatation of the bronchioles in such extensive areas that the whole of both lungs may assume a worm-eaten or honey-combed appearance.

Symptoms.—The child is pale, emaciated, and suffers from a paroxysmal cough simulating pertussis. The sputum is usually swallowed, but later considerable pus may be vomited. The fever which is present at onset may later disappear for varying periods. In the latter stages cyanosis and clubbing of the fingers are observed. Fowler points out that in spite of the somewhat extensive disease the general condition may remain fairly good or improve.

Physical Signs.—The physical signs are principally auscultatory—scattered râles of all types, frequently with a metallic quality suggestive of cavitation. The breath sounds may be suppressed or they may take on a tubular or amphoric quality when the condition is associated with pneumonia.

Diagnosis.—The condition is differentiated from *acute disseminated tuberculosis* with difficulty. The lack of sputum makes it necessary to save and examine the vomitus. In acute bronchiolectasis the symptoms are less severe in proportion to the extent of the disease than in tuberculosis, and the general condition may improve while the signs of disease in the chest extend, a condition rarely observed in tuberculosis. The development of tuberculous cervical adenitis favors a diagnosis of tuberculosis. The two conditions—tuberculosis and acute bronchiolectasis—may be associated.

Prognosis.—The prognosis in acute cases is unfavorable. In some instances the disturbance develops into chronic bronchiectasis and lasts several years or longer.

Treatment is hygienic, dietetic, and symptomatic. Attention should be paid to the underlying condition.

Elmer H. Funk.

FOREIGN BODIES IN THE BRONCHI

A wide variety of foreign bodies—pins, tacks, small nails, screws, pieces of jewelry and toys, articles of food, pieces of bone, nuts, watermelon seeds, peas, beans, teeth, dental fittings, etc.—have been aspirated, usually by children, into the tracheobronchial tree. Carelessness on the part of parents and the pernicious habit of using the mouth as a sort of hold-all are the principal reasons for such accidents. The foreign body may lodge in the larynx or trachea, or pass into the bronchus; it enters the right side in about two-thirds of the cases. The pathological and clinical changes which follow depend upon the size and character of the foreign body, the degree of obstruction to the air currents and secretions, and the type of superimposed infection. A pin has been known to enter the bronchus without causing even a cough; while intense, rapidly developing septic tracheobronchitis and purulent pneumonia have caused death in the course of a few days after aspiration of a peanut. The phenomena attending the lodgment of a foreign body are more severe in children than in adults.

Morbid Anatomy.—A metallic, non-obstructive foreign body induces local changes of slow evolution, which are influenced by the presence or absence of infection. Organic foreign bodies, such as peanuts and seeds, cause rapidly spreading, purulent tracheobronchitis, which leads to purulent pneumonia. If the bronchus is completely obstructed, the corresponding lung collapses or, as is more commonly the case, shows evidence of accumulated secretions and edema—a condition which Jackson speaks of as "drowned lung." If the obstruction is partial, and air can pass on inspiration but not on expiration, an obstructive emphysema results. In other instances obstruction to both inspiration and expiration is incomplete, varying amounts of air enter, and secretions accumulate in the lung from time to

time. The condition is chronic; there is a tendency toward abscess formation and bronchiectasis. A striking feature which has been emphasized in Jackson's work is the remarkable disappearance of pathological changes following bronchoscopical removal of foreign bodies, even though a long interval has elapsed since aspiration.

Symptoms.—The initial symptoms—choking, gagging, and coughing—may escape notice in a child; and in both children and adults may be followed by a symptomless interval during which the initial episode may be forgotten. Sudden death from asphyxia may follow the impaction of a foreign body in the larynx or trachea. Ordinarily *a foreign body in the trachea* is movable and the patient may be conscious of the movements. The obstruction from the foreign body *per se* and from traumatic subglottic edema gives rise to shortness of breath and wheezing. The cough is harsh and distressing, often paroxysmal, and productive of a varying quantity of mucoid and mucopurulent sputum which may be swallowed by young children. A striking feature is the sudden stoppage of cough or of an ordinary expiration when, on sudden ascent, the foreign body impinges on the glottis. Pain is uncommon. The "asthmatoid wheeze" of Jackson may be heard on expiration when the ear or the bell of the stethoscope is placed near the patient's mouth. Palpation and auscultation not infrequently reveal over the trachea a "slapping" or "fluttering" due to the movement of the foreign body. *In the bronchi* a non-obstructive metallic foreign body may produce but few symptoms for weeks and months. Sooner or later, however, local irritation and bronchial obstruction produce symptoms of bronchitis, atelectasis, edema, and eventually pulmonary abscess. Insidiously in some cases and more rapidly in others, cough and expectoration develop, hemoptysis may occur, and eventually fever, loss of weight and strength, and clinical manifestations not unlike those of pulmonary tuberculosis.

When a *vegetable organic foreign body*, such as a peanut kernel, bean, or watermelon seed, lodges in the trachea or bronchi a violent reaction ensues—distressing cough, dyspnea, irregular fever, leukocytosis, and rapid prostration. The severity of these symptoms is usually in inverse proportion to the age of the child. The term *arachidic bronchitis* was introduced by Jackson to designate the disturbance caused by peanuts, but the symptoms produced by other nuts, peas, beans, etc., are not dissimilar.

Physical Signs.—As McCrae has pointed out, the physical signs are varied and changeable. In the chronic cases they may be very few. In many patients limitation of motion on the affected side is the only finding. This is caused by non-obstructive foreign bodies, such as pins and needles. With bronchial obstruction the signs usually elicited are limited expansion, decreased vocal fremitus, impaired percussion resonance, and diminished breath and voice sounds. The "asthmatoid wheeze" may be elicited and at times fine "tissue paper" crackling sounds. With the development of abscesses and bronchiectasis the signs are those typical of these conditions. When, in the presence of an organic foreign body, obstructive emphysema develops there is diminished expansion, tympany, and a lack of voice and breath sounds; if the lesion is large, the heart is displaced toward the unaffected side. In all cases there *may* be auscultatory signs on the unaffected side which are due to extension of inflammation, shifting of secretions, or shifting of the foreign body.

Diagnosis.—A negative history and symptomless interval may be misleading. In the acute cases *diphtheria, influenza*, and *pneumonia* may be suggested by the symptoms, but can usually be ruled out by a careful history, the nature of the symptoms and signs, *x*-ray plates, and bronchoscopical studies. *Tuberculosis* is often confused with the chronic cases, but the history, basal location of the signs, negative sputum, and *x*-ray findings should make the diagnosis easy. The *x*-ray is invaluable in the direct diagnosis of opaque foreign bodies; the presence of obstructive emphysema after lodgment of the non-opaque bodies produces characteristic signs which the skilled roentgenologist recognizes as indirect evidence of the presence of a foreign body.

Prognosis and Treatment.—When the foreign body is not removed the prognosis is grave. In about 2 per cent. of cases the body is coughed up spontaneously. In the remaining 98 per cent. recovery almost invariably follows the bronchoscopical removal of the foreign body. Among Jackson's patients 98.3 per cent. recovered. In 44 cases complicated by bronchiectasis or abscess, Jackson reports recovery in 42 (94.4 per cent.). The treatment of foreign body in the tracheobronchial tree is obvious. Bronchoscopy should not be attempted except by skilled hands. When properly performed the risks are almost nil.

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Diseases of the Lungs

CIRCULATORY DISTURBANCES IN THE LUNGS

CONGESTION

Pulmonary congestion may be either active or passive in character.

Active Congestion.—Occurrence and Etiology.—Active congestion, or pulmonary hyperemia caused by an oversupply of arterial blood, may be

the result of such pulmonary infections as pneumonia, especially in the first stage of consolidation; bronchitis; pleurisy; tuberculosis, especially near active lesions; and other acute fevers. It also follows the inhalation of very hot air or irritating gases. In the latter type of case the symptoms of congestion may not appear until several hours after exposure to the gas. Active congestion due to acute venous stasis may be the result of acute cardiac failure. Intense active congestion of the lung may also develop in association with drunkenness, especially if the patient is exposed to extreme heat or cold. Such disturbances may prove fatal rapidly, *i. e.*, within twenty-four hours. An almost hemorrhagic congestion may follow violent exertion and prove fatal. (Osler calls attention to the lack, in these autopsy reports, of any description of the heart.)

Whether or not an active hyperemia may be an independent primary affection (*la maladie de Woillez* of French writers) is a disputed question. Certainly the symptoms and signs described as characteristic of "Woillez disease" (chill, pain in the side, dyspnea, cough, a temperature of from 101° to 103° F., defective pulmonary resonance, feeble breath sounds, sometimes bronchial in character, and many fine râles) would suggest larval pneumonia.

Symptoms.—The onset of acute pulmonary congestion is indicated by the addition of dyspnea and cough to the symptoms of the primary disease. If congestion is intense there is always some pulmonary edema, and the patient expectorates a frothy, often blood-stained, sputum.

Treatment.—The treatment of acute pulmonary congestion should be that of early pneumonia, into which, indeed, it may later develop: rest in bed, liquid diet, and free purgation. If there is a sense of oppression or thoracic constriction and the patient is not anemic, *venesection* gives relief. *Counterirritation* by Paquelin cauterization, dry cupping, and application of mustard poultices until the skin is just red is also helpful. *Tincture of aconite* is much used (3 drops every fifteen minutes until the heart is slowed) to depress the heart and consequently to lower the pulmonic circulation. The intravenous injection of *calcium chlorid* might well be tried. Small doses of *morphin* quiet the pain.

Chronic Passive Congestion.—In chronic passive pulmonary congestion the lung capillaries are continuously overfilled with venous blood. This condition may be either mechanical or hypostatic in character.

"Mechanical" Passive Congestion.—A *mechanical passive congestion* obtains if for any reason the return of the blood from the lungs to the heart is obstructed. Such is the case in affections of the left heart, particularly in mitral stenosis, but also in mitral insufficiency and in myocarditis. The course of these cardiac disturbances is frequently interrupted by brief periods of acute passive congestion with slight pulmonary edema which is superposed on the almost permanent chronic passive congestion and causes paroxysmal dyspnea (cardiac asthma). There is a belief that in such cardiac cases the chronic venous congestion of the lungs is by no means as mechanical as is usually supposed, but represents rather a protective device designed to relieve the heart by pooling a considerable volume of blood in the capillary bed of the lungs and thus definitely reducing the volume of the circulating blood. It is therefore the physiological equivalent of hemorrhage or venesection. Chronic passive pulmonary congestion may develop also whenever the pulmonary circulation is impeded, as it is during

hypertrophic pulmonary emphysema, sclerosis of the lungs, and mediastinal tumors which obstruct the pulmonic veins by pressure. A similar congestion develops in collapsed areas of lung when the venules are kinked so that the venous flow is obstructed.

Morbid Anatomy.—Lungs which have suffered chronic passive congestion are voluminous at autopsy. They feel dense and inelastic; have lost their bluish color, and are pale or have turned a typical russet brown color ("brown induration of the lung"). They are sometimes dry; sometimes edematous, and become pitted by pressure. They cut and tear with great difficulty because of an increase of the smooth muscle in the septa and of connective tissue in the alveolar walls. The cut surface at first has a brownish-red tinge, but on exposure to the air the hemoglobin is oxidized and the cut surface rapidly becomes vivid red. There is evidence also of degeneration and desquamation of the alveolar epithelium and of slight transudation from the tense capillaries of serum, often containing red cells, the hemoglobin of which is taken up by phagocytes and transformed into hemosiderin. It is because of the malnutrition of such chronically congested lungs that hemorrhagic infarctions are possible in this condition only. In long-standing cases the pulmonary artery and its branches often show arteriosclerotic patches.

Symptoms.—A chronic passive congestion of even marked grade may in cardiac cases give no pulmonary symptoms as long as compensation is well maintained. This is surprising when the increased rigidity of the lung tissue and the marked overfilling of the capillaries is considered. In other cases, however, the slowing up of the pulmonary circulation and the resulting difficulties of aëration favor the production of dyspnea and explain the marked tendency to attacks of bronchitis, frequently with blood-stained sputum. It is these pulmonary symptoms in cases of unrecognized mitral stenosis which frequently lead to error in diagnosis (*e. g.*, the "pseudo-tuberculous type of mitral stenosis"). With developing decompensation, however, the pulmonary symptoms become more marked. These are dyspnea, cough, and expectoration of sputum which may for a long time be uniformly rusty or marked by rusty streaks and dots which, microscopically, consist of masses of characteristic heart-failure cells, *i. e.*, alveolar cells filled with yellow pigment. In such cases the sputum frequently is definitely blood-tinged, while small pulmonary hemorrhages are common.

Hypostatic Passive Pulmonary Congestion.—*Occurrence and Morbid Anatomy.—Hypostatic passive pulmonary congestion* is quite different from the mechanical form of congestion. The former develops during protracted fever, *e. g.*, typhoid fever, and in those adynamic states which result from long debilitating illnesses. In such cases at autopsy the posterior portions of the bases of the lungs are very dark in color and so engorged with blood and serum that the alveoli may no longer contain air ("pulmonary splenization" or "hypostatic pneumonia"). Long-continued hypostasis may so lower the resistance of the lung tissue to infection that true inflammation (hypostatic pneumonia) results. Gravitation doubtless determines the localization of this congestion, but such a condition does not develop in healthy persons no matter how long they may remain in bed.

Hypostatic congestion may develop also as the result of the compression of the bases of the lungs by ascites, meteorism, and abdominal tumors.

In cases of cerebral apoplexy and of injury or organic disease of the

brain the bases of the lungs may be so deeply engorged that, on section, blood and serum drip from them; but they never are quite airless. In cases of hemiplegia this congestion is occasionally most marked on the hemiplegic side, and may even be confined to it. In such instances the lung tissue may have a blackish, gelatinous, infiltrated appearance, somewhat resembling diffuse pulmonary apoplexy.

Extreme grades of a similar condition have been found throughout the lungs of victims of morphin poisoning.

In any case of prolonged coma associated with hypostatic congestion one is apt to find also patches of consolidation due to the aspiration of particles of food into the air passages.

Symptoms.—The symptoms of hypostatic congestion are not at all characteristic; they are shortness of breath and cough with abundant sputum containing "heart-failure cells." On physical examination, percussion may reveal slight dulness, while on auscultation feeble, sometimes blowing, breath sounds with liquid râles are heard.

Treatment.—The treatment of hypostatic passive congestion is that of the condition causing the disturbance. For the intense pulmonary engorgement encountered in heart disease and in emphysema free bleeding is advocated. From 20 to 30 ounces of blood should be taken. If the blood does not flow freely, and the condition is desperate, the right auricle may be aspirated.

PULMONARY EDEMA

Pulmonary edema, or the transudation of serum from the engorged alveolar capillaries into the air cells and the alveolar walls, may be a general or a local condition. Transudation into the air cells is best illustrated by cases of cardiac failure during the few hours before death. In other cases, especially those with cardiovascular disease, *e. g.*, myocarditis, arteriosclerosis, chronic nephritis with arterial hypertension, and those with angina pectoris, the attacks of edema may be transitory. Some patients have repeated transitory attacks of edema (paroxysmal pulmonary edema).

Etiology.—According to the generally accepted theory of Welch, cardiac pulmonary edema is due to a relative weakness of the left ventricle which develops slowly and causes the blood to accumulate in the lung capillaries under steadily increasing pressure until transudation occurs. According to this view the edema is produced by intense, acute, active and passive pulmonary congestion. Others, however, regard it as the result of an increased permeability of the lung capillaries caused by disturbances of the vasomotor mechanism of the lungs; while still others think it is inflammatory in nature.

Pulmonary edema develops as a terminal event in some infections, such as pulmonary tuberculosis; in pregnancy; in angioneurotic edema; as a complication of an epileptic fit; and after thoracentesis if too much fluid (more than 1 liter) is removed at one time, even though slowly; or if a smaller amount is removed too rapidly. Attacks of acute edema without obvious cause may recur, as in Steven's patient, who had 72 attacks in two and a half years.

Morbid Anatomy.—The generally edematous lung is found at autopsy to be anemic, heavy, and sodden. It pits on pressure, and when incised large quantities of clear or blood-tinged serum flow from it. It may in places have a gelatinous aspect.

Symptoms.—The onset of acute edema is sudden, and is manifested by a feeling of oppression and pain in the chest, and rapid breathing which soon becomes dyspneic or orthopneic. There may be an incessant short cough; and a copious, frothy, sometimes blood-tinged expectoration may gush from the mouth and nose. The face becomes pale and covered with a cold sweat; the pulse is feeble and the heart's action weak. Over the entire chest piping and bubbling râles may be heard. An attack may be fatal in a few hours, or may persist for twelve or twenty-four hours and then disappear. When fatal, the edema usually develops slowly and insidiously with coma, and is manifest at first by coarse moist râles throughout the chest which soon obscure all other lung and heart sounds and later become audible even at a distance (the so-called "death rattle"). In the advanced stages streams of foamy serum may slowly pour from nose and mouth.

Treatment.—In treating this condition early *venesection* may be most helpful, also artificial respiration, dry cupping, and the inhalation of oxygen, if the patient is cyanotic. Following the method used in resuscitating a drowned person, the patient may be placed on his chest and abdomen with the foot of the bed raised. Early in an attack *ammonia* certainly has helped. *Morphin* is theoretically contra-indicated, but practically is very valuable and should be given hypodermically ($\frac{1}{4}$ grain—0.016 gm.). The dose may be repeated in fifteen minutes if there is no change. *Atropin* alone is of little value, but combined with the morphin may be especially useful in treating the edema due to toadstool poisoning or to pilocarpin, for it is said to be an antidote for these toxic substances. Since in the cardiac cases an increase of blood-pressure has been found to accompany, and perhaps to cause, the edema, the *nitrites* will be found of value and should be given until the blood-pressure actually falls. If, however, the arterial pressure is low, they should not be used, but rather *digitalis*, *ouabain*, or *adrenalin*. *Aromatic spirits of ammonia* (3j) may be given by mouth. *Calcium chlorid intravenously* (5 c.c. of a 5 per cent. solution) has been tried with success in 22 cases by John. Patients who have repeated attacks should be warned against overexertion. In congestion following thoracentesis the previous intrapleural pressure should be restored at once by producing an artificial pneumothorax on the side from which the fluid was removed.

PULMONARY HEMORRHAGE

Pulmonary hemorrhages are of two types: in one the blood pours into the open bronchi or into an open pulmonary or bronchial cavity and is expectorated either as pure blood or mixed with the sputum (bronchopulmonary hemorrhage or bronchorrhagia); while in the second it passes into the air-cells and lung tissue and is consequently not expectorated as blood, but rather as blood-stained sputum or as sputum stained by pigments from the modified hemoglobin (pulmonary apoplexy or pneumorrhagia).

Bronchopulmonary Hemorrhage.—Bronchopulmonary hemorrhage, or hemoptysis, or the "spitting of blood," is associated with a variety of conditions: The hemoptysis which occurs infrequently in *young healthy persons*, who neither at the time of the attacks nor in later years develop any other symptom or physical sign indicative of pulmonary disease, is a much disputed symptom. This may occur without warning, may be a single event, or may continue for a few days and then disappear, leaving no ill traces. Undoubtedly the great majority of such attacks are due to

tuberculosis. Although no definite proof of the infection may be obtained, most patients should at once be treated for tuberculosis. In one report from the Prussian Army hemoptysis was noted in 900, or 0.045 per cent. of the soldiers, all of whom were apparently healthy young men. Of these 900 cases, 480, or 54 per cent., could not be adequately explained, although 417, or 86 per cent., were probably tuberculous, and 221, or 46 per cent., were quite certainly so.

Hemoptysis occurs at some time in from 60 to 80 per cent. of all cases of *pulmonary tuberculosis*. It is unusual in children and in the early acute stages of the disease in adults. It is most frequent in women near or at the menstrual period. Some tuberculous patients have so many hemorrhages that they may be included in the so-called "hemoptysical" group. Among the immediate causes of such bleeding may be cited the increased activity of the tuberculous process, any acute superimposed respiratory infection due to *pneumococci* or *streptococci*, and ordinary colds, which are also most important. Exertion is perhaps not as important as the stasis or congestion due to rest, since in 69 per cent. of Bang's cases (quoted by Landis) the hemorrhage came on while the patients were at rest.

A pulmonary hemorrhage is not infrequently the very first symptom of an unsuspected tuberculous lesion. Landis states that of the 5856 patients with pulmonary tuberculosis seen at the Phipps Institute, 2790, or 47.6 per cent., gave on the first visit a history of hemoptysis. In such cases the quantity of blood lost is usually small and is mixed with the sputum; about 1 ounce of blood may be raised. It comes from a pulmonary vein and is bright red in color. The hemorrhages resemble those of early pneumonia and result from the escape of blood by diapedesis through a very congested mucosa, or from superficial ulceration. If larger quantities are raised the sputum for the following several days is streaked with blood or contains small dark red clots.

In the later stages of tuberculosis the hemorrhages are more profuse and result from the rupture of an artery in the wall of a tuberculous cavity or in a trabecula which crosses its lumen. It is not the artery itself which ruptures, but a small miliary aneurysm in its wall which has developed at a point previously weakened by the disease. Such hemorrhages explain only 8 per cent. of the deaths from tuberculosis. The gush of blood, which is dark in color because it comes from a pulmonary artery and is unmixed with sputum, may flow from the mouth almost without the aid of coughing. Warning of these large hemorrhages from cavities may be found in the appearance of slight blood-stains in the sputum.

Hemoptysis may occur in *several diseases of the lung*. In the initial stage of *acute lobar pneumonia* brisk bleeding may be the first symptom, but care should be taken to exclude the possibility of acute tuberculous pneumonia. The same is true in the early stages of *typhoid fever* with pulmonary congestion. Hemoptysis may occur during *whooping-cough*; and sometimes in malignant types of the *specific fevers*, the so-called hemorrhagic type, also in *purpura hemorrhagica* and such other "blood diseases" as *hemophilia*, *leukemia*, and *scurvy*.

Hemorrhages may be a conspicuous feature of certain *chronic pulmonary diseases: bloody bronchitis*, for example, and *cancer* of the lung and bronchi, when the sputum may be quite bloody; *pulmonary gangrene*, in which it may occasionally be fatal; pulmonary abscesses; over one-half the cases

of bronchiectasis, in which it is sometimes recurrent and very severe; actinomycosis; pulmonary tumors and cysts of the lung; and lung-fluke disease.

In many *heart affections*, particularly in mitral lesions, especially mitral stenosis, hemorrhages are common. They usually are slight, but may be profuse and may recur at intervals for years, each followed by definite relief of symptoms.

Repeated hemorrhages often accompany the *bronchial colic* due to expulsion of pneumoliths and bronchioliths. This *hemoptysis calculosa* is caused by direct trauma of the mucosa.

Small hemorrhages may result from the *rupture of a pulmonary* or *mediastinal abscess* into a bronchus.

Vascular degeneration, such as that of emphysema and arteriosclerosis, may produce bleeding.

In *ulcerative affections* of the larynx, trachea, or bronchi, if a large branch of the pulmonary artery is eroded, the hemorrhage may be profuse and even rapidly fatal.

An *aneurysm* which bursts into the trachea or primary bronchi may cause sudden and rapidly fatal hemoptysis. Of the 592 aneurysms of the thoracic aorta observed by Leman, 160 perforated into the left bronchus, pleura, or lung; and 62 into the right bronchus, pleura, or lung. In some cases of large aortic aneurysm the slight bleeding, which may continue for weeks or months, may come from the aneurysm itself, but more often from the bronchial mucous membrane or from the lung which has become congested or ulcerated because of the pressure of the aneurysm. Sometimes, however, it is the sac itself which "weeps" through the exposed laminæ of fibrin. The symptoms in these cases of hemoptysis—cough and dulness on percussion over one upper lobe—are easily mistaken for evidences of tuberculosis.

Pulmonary hemorrhage may be a manifestation of the *vicarious menstruation* which rarely follows interrupted normal menstruation; or it may recur periodically after the removal of both ovaries; or may be quite unexplained by any lesion even when the hemoptysis which has developed during menstruation proves fatal.

Hemoptysis, sometimes profuse and lasting for days, may recur at frequent intervals when the *blood-pressure* is high or when there are *gunshot injuries* and *foreign bodies* in the lung.

In hysteria the sputum sometimes contains blood (*hysterical hemoptysis*) which is probably derived from the mouth or pharynx.

Symptoms.—Hemoptysis appears, as a rule, suddenly, often without other warning than the desire to cough or the sudden presence in the mouth of a warm, salty fluid. The slight hemorrhages may be single, or may recur for days, and cause the sputum to be blood-tinged for several more days. In sharp contrast to these are the hemorrhages which follow erosion of a large vessel or the rupture of an aneurysm, either a miliary aneurysm of a pulmonary vessel or an aortic aneurysm rupturing through the bronchus, and may be so severe as to drown the patient.

Blood from the lungs usually differs from vomited blood, since it is alkaline in reaction, is frothy, and is mixed with mucus and air-bubbles. In it may sometimes be found blood-molds of the smaller bronchi. During a severe hemorrhage some blood is usually swallowed, much of this is later vomited, but some may blacken the stools after a day or two.

Prognosis.—Unless very profuse, as when due to rupture of an aneurysm into a pulmonary cavity, hemoptysis is not often immediately dangerous. In the great majority of cases the bleeding soon ceases spontaneously.

Treatment of Pulmonary Hemorrhage.—If the sputum is merely blood tinged, or if the quantity of blood lost is small, the hemorrhage may, by relieving congestion, be actually beneficial. *Rest, reduction of the blood-pressure* by a minimum diet, *purging* if necessary, and the administration of some preparations of *opium* to allay the cough are the main therapeutic measures to be advocated under these conditions. If the blood is brought up in very large quantities, however, it is almost certain that either a miliary aneurysm has ruptured or that a vessel has been eroded. When this occurs patients may pass rapidly beyond treatment, but, not rarely, they recover from the most profuse hemorrhage. The *fainting* induced by loss of blood is probably nature's most efficient means of promoting thrombosis, and it was on this account that patients were formerly bled from one or both arms.

Ligatures, or Esmarch's bandages, placed around the legs may serve temporarily to check bleeding. If the patient can be kept alive for twenty-four hours, a thrombus sufficiently strong to inhibit bleeding may form. All diet and previous medication should be stopped. If the affected side is known, the patient should lie on this side in order to protect the sound lung. The *ice-bag* is of doubtful utility, although when placed like a sand-bag against the affected side it may prove beneficial by immobilizing the lung. The patient may, if he wishes, suck ice. In protracted cases *pneumothorax* has been induced, sometimes with success. Rest of the body and peace of the mind, difficult to attain because of the frightened state of the patient, should be secured by the aid of hypodermic injection of *morphin* (gr. $\frac{1}{6}$—0.011 gm.) if necessary. In the majority of cases of mild hemoptysis these measures alone are sufficient; in many cases, indeed, the bleeding stops spontaneously.

Much of the more *specific drug therapy* is subject to criticism. Theoretically, it would seem desirable to reduce the frequency of the heart beats, to lower the blood-pressure, and to increase the coagulability of the blood. The drugs in common use seem to raise the peripheral blood-pressure and therefore actually to increase the total quantity of blood in the lung. This appears to be true of *digitalis* and of *ergot*, a very popular drug; while the *nitrites*, *tannic acid*, and *lead* are of little or no value. *Aconite*, on the other hand, seems definitely to reduce the pulmonary pressure and may therefore be helpful. *Pituitary extract* seems to be the only drug which, in the later stages of hemoptysis, raises the systemic pressure and simultaneously lowers that in the lung. *Alcohol* should never be given. One of the most satisfactory means of lowering the blood-pressure is purgation, and when the bleeding is protracted salts may be freely given. Subcutaneous or intramuscular injection of 6 to 10 c.c. of a 25 per cent. solution of *camphorated oil* often stops hemorrhage; also intravenous administration of 10 c.c. of a 10 per cent. *calcium chlorid* solution. Some physicians still require the patient to drink very slowly a glass of water containing a tablespoonful of *common salt* (NaCl). For the cough, which is always present and disturbing, *opium* should be given freely, and is, of all medicines, the most serviceable in cases of slight hemoptysis. If, however, the hemorrhage is profuse and there is real danger of the inundation of the bronchial

is transmitted by *Dermacentor venustis*. A form of *Rickettsia* found in great numbers in the lesions in the wall of blood-vessels and also in infected ticks is considered by Wolbach to be the etiological agent.

African "tick fever" or relapsing fever is transmitted by the tick *Ornithodorus moubata*, in which *Spirochæta duttoni* persists through successive generations.

Adapted Parasites (Ectoparasites) which Transmit Disease.—The "itch mite" (*Sarcoptes scabiei*) develops only on the skin of its host. Those of various animals are regarded as varieties of a single species. When transferred from animals to man, certain of these may cause more or less itching and irritation, but since they cannot breed except on their normal host they soon disappear. The male dies after copulation, but the impregnated female burrows into the epidermis and produces characteristic lesions, distributed chiefly between the fingers and toes, in the groins, axillæ, and on the external genitalia. These become more generalized in severe cases. The burrows are slightly colored by the eggs and excrement deposited by the female, and measure from a few millimeters to several centimeters in length. From fifteen to fifty eggs are deposited by each female, and a new generation is produced within about four weeks. This parasite is disseminated chiefly by contact or by any means which transfers the larvæ—adults or eggs. The latter are probably only rarely transmitted from host to host. Scabies assumed great importance during the recent World War and has been placed at the head of a group of diseases which caused about 90 per cent. of all sickness in one of the British armies. Sulphur ointment is commonly employed in the treatment of scabies. By employing the twenty-four-hour Danish method in scabies, it is possible to cure the condition by a single treatment. For details of the preparation of the ointment employed and the method of its application, it is best to consult special papers on the subject (Lomholt, 1920; Greenwood, 1924).

Linguatulidæ, or "tongue worms," so named from their characteristic shape, are related to the mites, but because of their adaptation to parasitism have lost nearly all resemblance to this group. The body is composed of a large number of segments, and on the head there are two pairs of claw-like hooks at the sides of the oral aperture. The adults live in the nasal cavity, chiefly of the dog and other carnivorous animals, and the eggs when deposited are discharged in sneezing. These develop when ingested by herbivorous animals and the larvæ enter the liver and other organs. As maturity approaches, the larvæ migrate through the tissues to the mucous surfaces, whence they leave their intermediate host in discharges from the respiratory tract or alimentary canal. This, however, does not appear to be an essential step in their transference, since they may be ingested in great numbers with the flesh devoured by carnivorous animals. The species most commonly found in man (*Linguatula rhinaria*) is relatively rare and is nowhere very prevalent in animals.

Lice assume great importance under conditions of war. Their presence is not only a source of annoyance to those not accustomed to them, but permits the spread of disease which may incapacitate and destroy great populations. Lice are wingless insects adapted to life on the surface of the body and feed upon the blood of their host. There are two types which live on man—the true louse (*Pediculus*) and the pubic or "crab" louse (*Phthirius pubis*). Two species of pediculi were formerly recognized, but since they

interbreed freely, they are now both thought to belong to one species, the *Pediculus humanus*, of which the body louse (*P. humanus vestimenti*) and head louse (*P. humanus capitis*) are varieties. The latter lives upon the scalp and attaches its eggs ("nits") to the hair; the former lives in the clothing and deposits its eggs there.

As the result of the irritation arising from louse bites, pustules and crusts may be formed in the scalp and the cervical lymph-nodes may become enlarged. Eczematous lesions may also develop and spread over the face and other parts of the body. Blepharitis and conjunctivitis are frequently associated with the head louse. As the result of the bites of body lice, more or less scratching is indulged in, which produces rather characteristically distributed excoriations and lesions. When neglected, the condition may become serious, in fact, many distinguished individuals are said to have died in past times of louse disease.

Pediculus humanus transmits typhus fever, relapsing fever (North African and European), and trench fever. The louse does not become infectious until eight or ten days after biting a typhus patient; after that interval the excrement or the crushed louse scratched into the skin produces infection. This is also true in the transmission of relapsing fever. The virus of this disease may be transmitted through several generations of lice. An individual may be infected with trench fever by the bite of infected lice (the usual manner of infection) or by inoculation of the skin with louse excrement in the process of scratching. The virus of trench fever is said to be filtrable.

Fleas (*Siphonaptera*) are wingless insects more or less related to and sometimes classified with the *Diptera*, or two winged flies. Their flat bodies enable them to pass through the fur of animals which they infest, and the marked development of the posterior pair of limbs enables them to make phenomenal leaps. The eggs are large and are deposited in the fur of the animal upon which they live, or in the shed fur and rubbish of animal haunts. The eggs of the human flea, for example, are distributed in dust and débris in the cracks of floors, etc. The larvæ, which are maggot-like, feed upon bits of organic material, especially the dried blood on the shed fur of infested animals; after a period of growth they spin a cocoon and enter the pupal stage. Being voracious feeders, the adults of some species die very quickly when removed from their hosts, but others live for long periods at low temperatures, especially when protected by dust and rubbish. Although the various species of fleas are each associated with a definite host, many feed to a large extent, as the occasion affords, on animals other than their normal host. During feeding, considerable quantities of blood may pass undigested through the alimentary tract, and when such dejecta dries upon hair or fur it serves as food for larval fleas.

The rat flea (*Xenopsylla cheopis*) is probably the most important agent in the transmission of bubonic plague. *Bacillus pestis* multiplies rapidly in the alimentary tract of this species, and it is said that infected fleas are abnormally active, moving from place to place rather than gorging themselves at one spot. It is quite generally conceded that infection of man is usually accomplished by inoculation of the skin with the excrement of the flea during scratching or rubbing. It is notable that cleanly habits, especially the daily bath, greatly diminish the chance of infection even though there may be exposure to infected fleas. It is said, however, that the

growth of bacilli in infected fleas produces more or less obstruction of the alimentary tract so that infectious material may be regurgitated into the bite wound. Other species that attack both man and susceptible animals may transmit the disease. Thus the human flea, *Pulex irritans*, the European rat flea, *Ceratophyllus fasciatus*, and the Californian squirrel fleas (*Hoplopsyllus anomalus* and *Ceratophyllus acutus*) are known to carry the infection.

Various measures are employed in destroying fleas, such as the destruction of animals which serve as hosts, strict adherence to habits of cleanliness, the filling of cracks, the use of naphthalene, or fumigation. Powdered sodium fluorid is a very effective destructive agent. Water is particularly useful in the prevention of the breeding of fleas, and, by the daily use of the hose, kennels and animal quarters may be kept comparatively free of these pests.

The "chigger," "jigger," or sand flea (*Dermatophilus penetrans*) attacks a variety of hosts, especially the human being and the pig. The impregnated female burrows into the skin, usually about the toes, and then becomes so greatly distended with eggs as to acquire the size of a small pea. The two posterior segments of the body plug the opening in the skin so that the eggs are discharged on the surface. The larvæ develop in dry sandy soil. Proper footwear and leggings to a large extent prevent the attacks of this flea.

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DISEASES OF ALLERGY

SERUM DISEASE AND SERUM ACCIDENTS

Definition.—Serum disease is an allergic reaction resulting from the parenteral administration of a foreign serum and characterized by an incubation period, skin eruptions, enlargement of lymph-nodes, fever, edema, and polyarthritis. It should be distinguished from the immediate shock-like, and sometimes fatal reactions, which occur when foreign serum is administered parenterally to an individual who is hypersensitive to the serum employed. These latter reactions are better called serum accidents. Since individuals manifest all degrees of hypersensitiveness from complete insensitiveness to a condition of extreme sensitization, transition forms between mild serum disease and severe serum accidents may occur.

History.—Although animal blood had occasionally been used in transfusions since the seventeenth century and various untoward effects noted, not until 1875 (Landois and Ponfick) was there any appreciation of the important difference between human and animal blood for transfusions. Generalized urticaria ten days after transfusion of alien blood was reported in 1874 (Dallera), but its significance was not understood. When diphtheria antitoxin came into general use in 1890 the symptoms of serum disease and serum accidents soon attracted wide-spread attention. At first they were ascribed to the antitoxin content and then to some other unknown constituent of the horse serum, but Johannessen (1895) showed that normal horse serum was equally effective. The first systematic study of the clinical and immunological phenomena of serum disease was undertaken by von Pirquet and Schick; their results were published in a monograph in 1905. Their work defined and illuminated the problem and has stimulated many others during the past twenty years to investigate the incidence, symptomatology, and mechanism of serum reactions.

Incidence.—Not every patient treated with serum develops serum disease. If amounts below 10 c.c. are used, only about 10 per cent. have symptoms, but if 100 c.c. or more are administered, only 10 per cent. escape at least some manifestation of serum disease. The incidence, therefore, depends largely upon the amount of serum given. Race is also a factor, but of less numerical importance. Negroes and American Indians are less susceptible than the white race. Age, sex, the disease for which serum is given, and the route of administration seem to have little or no effect on incidence. For some obscure reason the serum from certain horses produces serum disease more frequently than that from others.

Pathogenesis.—Precipitins for the foreign serum are usually in the circulation after the ninth or tenth day. In severe cases they are apt to reach a high titer, and in patients who, despite large amounts of serum, have little or no serum disease, they are usually absent, transitory, or of low titer. When the precipitin in the circulation reaches a high titer the foreign serum still in the circulation disappears rapidly; when no precipitin is demonstrable the disappearance of the foreign serum from the circulation is greatly retarded. The symptoms of serum disease are thought to be due to a union of the foreign serum with the specific precipitin which has been elaborated during the incubation period, but the possibility has not been excluded that the symptoms are an expression of the immune reaction involved in the production of antibody rather than the result of a union between antigen and antibody.

Symptoms.—When large amounts of serum are administered the *severity of the symptoms* is determined chiefly by the constitutional susceptibility of the individual. A liter of serum given during the course of two or three days may produce nothing more than a few urticarial wheals and slight enlargement of the superficial lymph-nodes for a day or two. Other patients, after receiving a few cubic centimeters of serum, may have severe urticaria, edema, fever, arthritis, and swollen tender lymph-nodes for one or two weeks. Exceptionally, the symptoms persist for three weeks or longer. In a large proportion of patients they subside after four to six days. When such amounts of serum as are commonly employed in diphtheria and tetanus immunization have been administered, the severity as well as the incidence of symptoms tends to be less than after the large amounts given for pneumonia (Type I) and meningococcus meningitis. But even after small quantities of serum given subcutaneously, an occasional patient may have severe and prolonged serum disease. The nature of the constitutional factor which determines to a large extent the incidence and severity of serum disease is quite unknown.

Serum disease without *skin manifestations* is very rare. The eruption is usually urticarial or a mixture of urticaria and erythema. Itching of the skin often comes first; then patches of erythema and discrete wheals appear; the wheals with a circumferential halo of erythema may remain discrete, or as the eruption becomes more intense large wheals, the size of the palm of the hand, appear, and by confluence form bizarre patterns over the chest, back, or extremities. The face is usually affected. Itching is often intense. Occasionally the eruption is morbilliform or scarletiniform, but these atypical varieties are more often seen during a relapse than during the initial sickness. Purpuric rashes are occasionally observed in serum disease of more than average severity. The eruption usually disappears after three to five days. When the serum has been administered subcutaneously or intramuscularly, the earliest eruption is apt to be at the site of the injection. It may remain confined to this area—the so-called local serum disease—or subsequently become generalized.

Slight or moderate enlargement of the *superficial lymph-nodes* is usually present. Often this is the first symptom, antedating the eruption by one or two days. The nodes may or may not be tender. Frequently the epitrochlears are the first nodes in which the enlargement can be felt. After the other symptoms of serum disease have subsided the nodes often remain enlarged for several days. When the serum has been administered under the skin or into the muscles the regional nodes are apt to be the first to increase in size. Slight enlargement of the spleen is not infrequent.

After large amounts of serum, 50 to 60 per cent. of patients with serum disease show some evidence of *arthritis*. In most cases objective changes are slight or absent. The patient complains of pain and stiffness, but there is little to be seen or felt. In a small proportion of cases the joints are swollen, hot, red, and distended with an exudate which has an interesting similarity to the joint fluid of rheumatic fever (Swift and Boots). It is turbid and contains leukocytes up to or above 20,000 per cubic millimeter. Polymorphonuclear cells usually predominate. A precipitin test often reveals the presence of horse-serum in the joint exudate. The commonly involved joints are the knees, ankles, elbows, wrists, and small joints of hands and feet. Less commonly the other joints are affected. The tem-

poromaxillary joints are involved more often in serum disease than in rheumatic fever. It is unusual for joint symptoms to appear at the onset of serum disease.

Fever occurs in about one-third of the cases. From an elevation of only 1 degree for a day or two, all gradations are observed. In severe cases the temperature may reach 103° or 104° F. every day for a week or ten days. It is usually an irregular and remittent type of temperature curve.

Edema occurs also in about one-third of the cases. The face, sacral and pretibial regions, ankles, hands, and arms are the areas where it is most often noted. Chlorid and water retention, a lowered phthalein excretion, moderate oliguria, albuminuria, and cylindruria are not unusual concomitants of the edema. Rarely, if ever, is there a measurable *nitrogen retention*. After the serum disease has subsided, all evidence of impaired renal function vanishes. Attempts to demonstrate horse serum in the urine have been unsuccessful. *Optic neuritis*, with a slight increase of the cells and globulin in the spinal fluid, may be observed occasionally.

In adults there is frequently no change in the *blood picture*. von Pirquet and Schick found that children show a leukocytosis during the incubation period, and leukopenia after symptoms develop. Such changes rarely occur in adults. Even severe cases may show nothing abnormal in the blood-count or there may be a mild leukocytosis while symptoms are present, and toward the end or after the period of symptoms an increase of the eosinophil cells.

Other symptoms occasionally observed without any other explanation than that they are a part of the serum disease are: abdominal pain, vomiting, diarrhea, stupor, headache, conjunctivitis, and sore throat.

Relapses occur, in our experience, after a free interval of from four to fourteen days. With a recurrence of symptoms the eruption is more apt to be erythematous, morbilliform or multiform than urticarial. Any of the other symptoms may be present. There are two observations supporting the belief that relapses represent reactions to antigenic constituents of the foreign serum different from those responsible for the initial outbreak of symptoms. Dale and Hartley showed that when an animal is sensitized to a foreign serum, sensitization to the serum albumin develops later than to the serum globulin, and Coca found no relapses in 129 patients with serum disease due to a diphtheria antitoxin consisting of the isolated pseudoglobulin.

Diagnosis.—Very rarely is there any difficulty in recognizing serum disease. Occasionally a relapse with an atypical or inconspicuous eruption may cause uncertainty. It is sometimes difficult to decide whether fever, occurring during or immediately after a serum eruption, is due to a complication of the disease for which the serum was given or to the serum disease. A leukocyte count below 12,000 or an eosinophilia is in such cases evidence in favor of serum disease.

Prognosis.—Fatalities from serum disease itself are unknown. Complete recovery, even from the severe forms, is almost invariable, provided the infectious disease for which the serum was administered leaves no permanent ill-effects. A high percentage of individuals retain for years some degree of sensitization to the serum employed; yet with proper precautions the same kind of serum can be administered subsequently to nearly all of these patients.

Treatment.—It has not been demonstrated that serum disease can be prevented. A certain amount of symptomatic relief is the most that can be expected. For the pruritis, calamine lotion containing 1 per cent. phenol is often helpful. Bicarbonate of soda baths may give temporary relief even in severe cases. Salicylates are ineffective in the treatment of the arthritis, but seem to mitigate the joint symptoms if given in large doses soon after the administration of the serum.

SERUM ACCIDENTS

Definition.—Serum accidents are the immediate, shock-like, sometimes fatal, reactions which occur in individuals who are hypersensitive to the serum administered.

Etiology.—The essential cause of these reactions resides in the specific reactivity of the individual. Persons susceptible to asthma or to rhinitis and coryza when in proximity of horses are most likely to have serious serum accidents. Those sensitized by a previous injection of serum may also have alarming or, rarely, even fatal reactions, but in general are less sensitive than the "horse asthmatic" group. Certain individuals also who have never experienced symptoms from contact with horses and who have not received a previous injection of serum, show a positive skin reaction to horse serum and hence must be considered hypersensitive.

Pathogenesis.—Despite certain dissenting opinions, most competent authorities look upon serum accidents as examples of anaphylaxis. The fact that the majority have occurred in spontaneously hypersensitive individuals upon the first injection of serum has been urged as a reason for separating this group of serum reactions from anaphylaxis. In those cases in which the first serum injection is tolerated without immediate symptoms and a subsequent serum injection after weeks or months has unloosed immediate and violent symptoms, the analogy with experimental anaphylaxis is nearly complete. The chief discrepancy is found in the phenomena of desensitization.

Symptoms.—The *onset* of symptoms may be lightning-like. Almost before the needle is withdrawn local itching and edema develop. A feeling of apprehension, generalized urticaria, often sneezing and a prickling sensation of the throat, edema of face, hands, neck, or perhaps of the whole body, cyanosis, choking sensation, cough, and violent asthma are common symptoms. The pupils dilate, the pulse becomes thready or imperceptible; the temperature rises; convulsions may occur, and the patient may be dead in less than ten minutes; in other fatal cases several hours may elapse between injection and death. If the serum accident does not terminate fatally, the symptoms may become those of serum disease at once or after a free interval of several days.

Treatment.—The *prophylaxis* of serum accidents consists of (1) recognition of those who are hypersensitive before administering serum; (2) desensitization of hypersensitive individuals.

A history of asthma or hay-fever should make one cautious in giving serum, particularly if the patient has experienced such symptoms when near horses or stables. A history of previous serum administration also calls for precautionary measures. An intracutaneous test with a 1 : 10 solution of horse serum should be made. If this is positive, the patient should be considered an unsafe subject for serum therapy by routine methods.

Desensitization offers a method of administering serum safely to many patients who would otherwise react violently or even fatally if the whole amount of serum were injected in the usual way. The genuine "horse asthmatic" may in some instances be so highly sensitive that he cannot be desensitized, but most of those whose hypersensitiveness dates from a previous serum treatment can, in the course of twelve to twenty-four hours, be rendered sufficiently tolerant to take therapeutic quantities without danger. If there is a history of asthma or a strongly positive skin test, the first desensitizing dose should be given *subcutaneously*. Beginning with 0.005 to 0.025 c.c. according to the intensity of the skin reaction, the dose may be doubled every half-hour until 1 c.c. is given. Then 0.1 c.c. is injected intravenously. Dilution with normal salt solution is advisable because thereby injection may be made more slowly. The *intravenous* dose should be doubled every twenty to thirty minutes until the required amount has been given. In case anything more than a mild reaction occurs one should wait the usual interval or longer, and then repeat the last dose which produced only a mild reaction or none at all. If the serum is to be administered *intraspinally*, the same procedure should be carried out until five or six of the intravenous doses have been given. Then with diluted serum the intraspinal route may be tried slowly and cautiously. With patients only slightly sensitive, as often proves to be the case when hypersensitiveness has been artificially produced by a previous serum treatment, the desensitization program outlined may be shortened by starting with a slightly larger dose and increasing the size of the doses a little faster.

One should always have on hand, when attempting desensitization, a syringe containing *epinephrin* ready for use. Epinephrin is a specific for serum accidents. Subcutaneous injection of 0.3 to 0.8 c.c. (5–12 minims) will usually prove effective in the milder accidents. Injection should be repeated after a few minutes if necessary. If the symptoms are alarming, larger doses are indicated. *Atropin*, gr. 1/60 to gr. 1/30 (0.001–0.002 gm.), subcutaneously, is also recommended.

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HAY-FEVER

(Atopic or Allergic Coryza)

The condition generally known as hay-fever, but more properly termed "atopic" or "allergic coryza," is a manifestation of the so-called hypersensitive reaction. The term *hypersensitiveness* is now used medically in a

restricted sense to indicate a certain group of biological reactions that occur in man and that are mediated by a special mechanism. They are not to be considered as toxic reactions, for the specific substance known as atopen or allergen, to which the reaction occurs, is not toxic for the normal individual. The reactivity depends upon a substance within the cells and in the serum of the hypersensitive man. In this chapter we are concerned solely with the reactions of the upper respiratory tract whose clinical manifestations are those of an irritative coryza with ocular manifestations. By far the greater number of cases of atopic (allergic) coryza are caused by pollens and, therefore, more particular attention will be paid to this group, designated as *seasonal hay-fever*, because the clinical symptoms occur with seasonal regularity. It must be borne in mind that the seasonal periodicity of these attacks is not due to any seasonal change in the specific reactivity of the individual. The clinical symptoms are intermittent merely because the contact with the pollen is intermittent. A second and by no means small group of cases has identical symptoms either continuously or intermittently throughout the year, and is called *perennial or non-seasonal hay-fever*. It corresponds with the group to which the term "vasomotor rhinitis" is applied. The perennial nature of the attack is due to the fact that the excitant or specific substance may be present at any and all times of the year. The mechanism of the reaction is the same in both groups.

SEASONAL TYPE OF HAY-FEVER

(*Rose Cold, Pollinosis*)

History.—The following facts stand out as important in the development of our present conception of the nature, the causative factors, and the treatment of hay-fever. Bostock in 1819 identified the seasonal coryza as a clinical entity. Elliotson in 1831 suggested the pollens as causative factors. In 1873 Blakeley, a hay-fever victim, used extracts of pollens upon himself and was able to precipitate an attack. Dunbar, conceiving that the pollen contained a toxic albumin, attempted to immunize horses against it. He believed that the serum of injected horses contained a specific antitoxin, and this immune horse serum was used in the treatment of hay-fever and sold under the trade name of "Pollantin." More recently it has been shown that this serum from supposedly immune horses does not contain any specific pollen antibody. Wolff Eisner in 1906 suggested that hay-fever was a specific anaphylactic reaction. Freeman and Noon in 1911 were the first to publish their results on the treatment of hay-fever by active immunization with pollen extracts. Clowes in 1913 reported on the specific reactions exhibited by hay-fever cases. Cooke in 1915 reported on 144 cases treated by injection with extracts of pollen. Since this time a very considerable amount of work has been done; the important pollens have been determined, and the technic of diagnosis and the method of treatment have been fairly well systematized.

Etiology.—In general, the air-borne pollens are the important etiological factors, but almost any pollen may be a factor when it is presented in sufficient concentration to the specifically sensitive individual. In the eastern part of the United States it is possible to distinguish three seasonal varieties of hay-fever. First, the *spring type* begins at the end of March or early April and extends to the end of May. This is due almost entirely to the pollens of trees, especially of the oak, elm, maple, birch, and hickory. The second type, beginning at the end of May and extending to the middle of July, is caused almost entirely by the pollens of grasses and is designated as the *summer type*. The important pollens in this group are timothy, redtop, June grass, orchard grass, sweet vernal, and plantain. The third or *fall type* begins in the middle of August and continues until frost. The pollens of the ragweeds are mainly responsible for this group.

Incidence.—Heredity is the only known factor in the pathogenesis of hay-fever.

Morbid Physiology.—In 1919 Ramirez reported what appeared to be a passive transfer of hypersensitiveness by means of blood transfusion. The donor was hypersensitive to horse dander and had clinical symptoms of coryza and asthma on exposure to horses. Following transfusion the recipient developed an attack of asthma after exposure to a horse. He had never had asthma prior to the transfusion. In 1921 Prausnitz demonstrated the fact that the serum of a fish-sensitive patient when injected intradermally into a normal man produced a localized skin sensitiveness to the same fish preparation, whereas the other areas of skin in the normal man showed no evidence of sensitiveness whatsoever. deBesche confirmed this observation of the passive transfer of sensitiveness, and more recently Coca and Grove have confirmed and extended these observations which establish the fact that the blood-serum of clinically sensitive cases contains a substance which reacts specifically with the atopen (allergen) to which the donor is sensitive.

The earliest observations on cases of human hypersensitiveness had long shown that the hypersensitive reaction can be demonstrated in the skin as well as in the mucous membranes of individuals with clinical hay-fever and asthma. This general skin sensitiveness is made use of in diagnosis.

Morbid Anatomy.—There is no organic pathology in uncomplicated seasonal coryza. The bony and cartilaginous structure and the mucous membrane of the nose may be as normal in appearance in patients with hay-fever during the free period as they are in the normal man. The only organic lesions which may be present are polypoid degeneration and secondary infection of the paranasal sinuses.

Symptoms.—The symptoms of hay-fever are essentially local, being due to the atopic reaction occurring in the mucous membranes of the eye, nose, and pharynx. These symptoms vary considerably in their severity according to the degree of sensitiveness of the particular individual. In occasional cases peculiar variations have been noted, such as those in which the symptoms are entirely nasal and there is no clinical ophthalmic reaction. Or, more rarely, one eye only is involved or one eye is much more sensitive than the other. During the attack the symptoms vary greatly in severity from day to day or even from hour to hour. They consist of an *itching* and *congestion*, sometimes even of an edema, of the mucous membrane of the sclera and conjunctiva. *Photophobia* of greater or less degree results. There is itching of the nose, sometimes even of the skin over the nose and of the face. *Sneezing* occurs in paroxysms, is violent, and is accompanied by a thin, alkaline, irritating, serous discharge. Congestion and edema of the mucous membrane of the nose occurs, and when the edema is great there may be complete obstruction to nasal breathing. Itching is often felt in the ears, on the roof of the mouth, and in the pharynx.

The clinical picture of seasonal hay-fever is quite typical. It is particularly characterized by its strict seasonal occurrence and by the fact that in any given individual the attack from year to year begins and ends on approximately the same date. This is quite readily explained by the fact that in any given locality the pollination of any particular plant is very little influenced by weather variations.

One important point with regard to all cases of hypersensitiveness must

be borne in mind, namely, that over 50 per cent. of the patients are hypersensitive to more than one atopen. As a matter of fact, approximately 33 per cent. of the patients with the summer type of hay-fever are sensitive also to the pollen of ragweed, so that it is not uncommon for seasonal hay-fever to begin in the spring and continue throughout the summer. The essential point is that attacks do not occur during the winter months. On the other hand, a form of seasonal hay-fever is not infrequently combined with the perennial types of coryza to be described later. There may be a perennial disturbance, with exacerbations occurring in the spring or summer or fall. These complex manifestations can only be recognized by means of the diagnostic tests. Occasionally typical seasonal hay-fever, the fall type for example, does not cease at the time of frost, but continues into the winter. This may be the result of an additional atopic reaction, or of secondary sinus infection.

Complications.—*Multiple atopic reactions* are to be considered as complications of typical hay-fever. They can only be differentiated by careful diagnostic skin tests.

Infection.—Infections of the paranasal sinuses occur in a large percentage of cases, but in only a relatively small percentage does this infection become clinically important and warrant special treatment.

Asthma.—There is one type of asthma which is strictly atopic and caused by the hypersensitive reaction in the bronchial mucous membrane. Here the attack is as typically seasonal as hay-fever. Usually in these cases the asthmatic manifestations do not begin until the symptoms of hay-fever have been present for about two weeks. Asthma of this type occurs in about 15 per cent. of all cases of hay-fever. There is also a type of asthma which results from infection of the paranasal sinuses. This form usually develops late in the course of the attack of hay-fever and may persist long after the seasonal limits for hay-fever.

Pollen Preparations.—Of the many methods of preparing and standardizing the pollen extracts, the most satisfactory is that in which the extract used for therapeutic injections is identical with that used for the cutaneous and ophthalmic test. Extracts containing glycerin and alcohol cannot be used in this way. The best method of preparation is that published by Coca in which the extract is standardized by the nitrogen content. From the stock extract the following dilutions are made for test and treatment:

Solution	1	contains	0.00001	mgm.	of	nitrogen	per	c.c.
"	2	"	0.0001	"	"	"	"	"
"	3	"	0.001	"	"	"	"	"
"	4	"	0.01	"	"	"	"	"
"	5	"	0.1	"	"	"	"	"

Gradual deterioration of these pollen extracts is a difficulty that has not been overcome. As it is probably due to enzyme action, great care must be exercised in keeping the extracts cold during preparation and throughout the period of use. When proper attention is paid to these details the extracts are entirely satisfactory for about six months. The methods of collection of the pollens will not be discussed here since satisfactory preparations of the important ones may now be obtained from reliable sources.

Diagnosis.—The determination of the specific pollens to which an individual may be sensitive is carried out by means of cutaneous and ophthalmic tests.

1. Cutaneous Test.—The cutaneous test may be performed in two ways. In the *scarification method* the desiccated or fluid extract of pollen or the pollen itself is applied to a small scarified area of the skin. In the *intradermal method* the extract of pollen is introduced into the most superficial layer of the skin through a fine hypodermic needle (26 gauge). The

amount injected in any one test is about 1/50 to 1/100 c.c. This forms a small papule from 2 to 3 mm. in diameter. Using either method, from six to eight tests may be made at any one time. The intradermal method is the more delicate and accurate of the two, but for anyone not experienced in the use of the tests the scarification method is perhaps the safer.

Tests are negative when there is no increase in the size of the original papule, no zone of hyperemia, and no itching. *Positive reactions* are designated as "marked," "moderate," or "slight." In the *marked reaction* from five to fifteen minutes after the introduction of the extract there is the development of an urticarial wheal with irregular outline and pseudopod projections extending out into a zone of hyperemia. This wheal may vary from $\frac{1}{4}$ inch to several inches in diameter if the reaction is very marked. When the wheal exceeds an inch in diameter the subject is exquisitely sensitive to the extract in the concentration in which it was used, and a general or constitutional reaction may result. Itching practically always accompanies these reactions. The wheal usually fades within two to four hours and becomes blended with the surrounding zone of hyperemia, which may last from six to twenty-four hours. Occasionally, even at the end of thirty-six hours, there is still hyperemia and edema at the site of the test. *Moderately positive reactions* are merely less severe than the marked reactions. There is a decided increase in the size of the papule without the marginal irregularity or pseudopod formation characteristic of the marked reaction. There is usually a zone of hyperemia, and itching. Such reactions usually fade entirely within two to four hours. A *slight reaction* is indicated by very little increase in the size of the original papule. There is a small zone of hyperemia, and itching may or may not be present. Such manifestations fade in one to two hours.

Absolute reliance cannot be placed upon the positive skin test in the diagnosis of a clinical hay-fever. A marked positive reaction that can be verified at will is pathognomonic only of a cutaneous hypersensitiveness. The ophthalmic reaction to be described later is used for the determination of the hypersensitiveness of the mucous membrane.

Titration of Sensitivity.—As there is a very striking variation in the reaction of different individuals, it has been necessary to estimate quantitatively the degree of sensitiveness. This consists really of a titration *in vivo* of the amount of reacting substance present in the cells and serum of the patient. This principle of titration may be carried out with the ophthalmic test, but experience has shown that the reaction of the skin is a truer indication of the degree of general sensitiveness. The patient is first tested with solutions 2 and 3. If solution 2 causes marked reaction he is then tested with solution 1. If solution 2 or 3 does not produce a marked reaction solution 4 is used. On the basis of such tests cases are classified as follows:

Reaction to solution.*	Class A.	Class B.	Class C.
No. 1	Moderate.	Slight.	Negative.
No. 2	Marked.	Moderate.	Slight.
No. 3	Marked plus†	Marked.	Moderate.
No. 4		Marked plus.†	Marked.

* The strength of these solutions is given on previous page.
† "Marked plus" means that the wheals are over 2.5 c.mm. in diameter.

2. Ophthalmic Test.—In the ophthalmic test a drop of the same pollen extracts as are used in the skin test is instilled into the con-

junctival sac of the eye. When the *reaction is negative* there is no change. A *positive reaction* is indicated by itching of the eye, lacrimation, and congestion of the scleral and conjunctival mucous membrane. In some cases the pollen extract is carried into the nose through the nasal duct and causes a nasal reaction, with sneezing, itching, and serous discharge. A positive ophthalmic test is pathognomonic of clinical hypersensitiveness and for this reason is important in the determination of the specific atopen (allergen). As to the relative value of the cutaneous and ophthalmic test, the positive ophthalmic reaction may be considered a sign of mucous membrane hypersensitiveness and indicates that whenever the patient comes in contact with this atopen under natural conditions a reaction is bound to ensue. The ophthalmic test is not as delicate as the cutaneous and only a limited number can be made. Furthermore, this test cannot be employed during an attack. The cutaneous test serves better for the titration of the degree of sensitiveness and has not the technical limitations of the ophthalmic reaction.

The first important point in the diagnosis of hay-fever is to obtain an accurate history of the time of onset and offset of the attack. From this history information as to the probable specific factor is gained; but one should always bear in mind the fact that multiple sensitizations are present in about half of the cases, and it is therefore wise to test with the more important substances that are causative factors in the perennial types of hay-fever. (See *Non-seasonal Hay-fever.*) If a reaction is obtained to one of the grasses the reactions to all other pollens of grasses will be of about the same degree. If a patient reacts to one of the varieties of ragweed, a similar reaction is always obtained from the others. The same cannot be said, however, for the pollens of trees, because no uniformity of reaction has been found except with species of the same genus. For this reason all of the more important tree pollens must be tested if the patient's history indicates hypersensitiveness to this group.

Treatment.—Climatic.—There is no particular locality in which the patient suffering from the *spring* or *summer type* of hay-fever may be assured of complete relief except upon the ocean. Patients suffering with the *autumnal type* may avoid the attack in the White Mountains, on the coast of Maine, in Florida, California, and Europe.

Drug Therapy.—Cocain, of course, temporarily modifies the attack, but except in cases of the utmost severity its use is not warranted. Epinephrin in the form of nasal sprays is usually irritative and produces a secondary reaction that is worse than the original condition.

Specific Treatment.—*Prophylactic.*—The specific treatment of hay-fever by means of pollen extracts is well established. Having first determined by means of the tests the proper pollen extracts to be used, and the degree of sensitiveness of the individual to these pollens, that is, having classified a patient according to the scheme previously outlined, treatment is begun with subcutaneous injections about ten weeks in advance of the expected attack. Increasing doses are given at approximately weekly intervals, according to Table 1.

The maximum dose which is attained at or about the period of clinical onset is maintained without further increase throughout the season. With the earlier doses there is usually some reaction at the site of injection, with swelling and itching lasting for twelve to twenty-four hours. If the local

TABLE 1

PROPHYLACTIC TREATMENT

Approximate Dosage According to Degree of Sensitivity

Number of injection.	Mgm. of N.		
	Class A.	Class B.	Class C.
1	0.00001 (*a*)	0.0001 (*b*)	0.0005
2	0.00002	0.0002	0.001
3	0.00004	0.0004	0.002
4	0.00007	0.0007	0.004
5	0.0001	0.001	0.007
6	0.0002	0.002	0.01
7	0.0004	0.004	0.015
8	0.0007	0.007	0.02
9	0.001	0.01	0.03
10	0.001	0.01	0.04
11	0.001	0.01	0.06
12	0.001	0.01	0.08
13	0.001 (*c*)	0.01 (*d*)	0.1 (*e*)

Notes.—(*a*) 1/10 c.c. solution 2. (*b*) 1/10 c.c. solution 3. (*c*) 0.001 continued weekly throughout the season. (*d*) 0.01 continued weekly throughout the season. (*e*) 0.1 continued weekly throughout the season.

reaction persists longer than forty-eight hours, the subsequent dose should not be increased for fear of a general reaction.

PHYLACTIC TREATMENT.—Phylactic treatment is necessary when patients apply for treatment during or just before the onset of the attack. Here the same method of diagnosis by means of the cutaneous test is necessary. The ophthalmic test is useless after the attack has begun. The injections are continued to the end of the season according to Table 2.

TABLE 2

PHYLACTIC TREATMENT

Approximate Dosage According to Degree of Sensitivity

Time.	Mgm. of N.		
	Class A.	Class B.	Class C.
1st day	0.00001	0.0001	0.0005
2d day	0.00001	0.0001	0.0005
3d day	0.00001	0.0001	0.0005
After 2 days	0.00002	0.0002	0.001
" 2 "	0.00003	0.0003	0.002
" 3 "	0.00004	0.0004	0.003
" 3 "	0.00006	0.0006	0.005
" 3 "	0.00008	0.0008	0.007
" 3 "	0.0001*	0.001*	0.01*

* This dose is continued every three to five days to end of season.

Constitutional Reactions.—These begin very quickly after the injection, sometimes within a few minutes, practically always within an hour. The sooner they begin the more severe and the more dangerous they are. The symptoms of the constitutional reaction are a general cutaneous erythema, urticaria, and itching, with marked coryzal symptoms both nasal and

ophthalmic. Occasionally there is edema of the eyelids and of the face. Asthma is the symptom that makes the reaction dangerous, and an asthmatic attack may begin even if there is no clinical history of asthma as a part of the hay-fever itself. These constitutional reactions should be immediately recognized and treated by liberal subcutaneous injection of epinephrin (1 : 1000 solution in amounts of 0.5–1.0 c.cm.). This should be repeated frequently in order to control the attack. If the attack is very severe the injection should be given intravenously. No limit should be put upon the dosage, for under these conditions enormous quantities are tolerated. *Morphin* is also indicated in the usual dose. In very severe attacks, when there is indication of dilatation of the heart caused by the intense dyspnea, *strophanthin* administered intravenously is helpful. At the onset of such an attack and when the injection has been given in an extremity, it is wise to apply a tourniquet very tightly above the site of injection in order to delay further absorption into the general circulation.

The reason for the beneficial results of the injection of pollen extracts has not yet been discovered. After a complete course of treatments the cutaneous and ophthalmic reactions are still obtained with about the same degree of intensity as before the treatment. The effects of the injections are not permanent. As a rule the course of treatment must be continued from year to year, although in general it is observed that the sensitivity tends to decrease after several years of treatment. Nothing approximating a permanent cure is assured. That the treatment is effective is demonstrated by the clinical results that have been obtained consistently over a period of ten years. In 80 to 90 per cent. of the cases treated the coryzal symptoms are almost entirely eliminated. It is very difficult to secure a complete absence of coryzal symptoms throughout the entire season. In those cases in which asthma occurs as a part of the atopic reaction the results are even more satisfactory. In over 50 per cent. of the cases with clinical asthma this symptom is entirely absent.

NON-SEASONAL TYPE OF HAY-FEVER

(Perennial Hay-fever, Vasomotor Rhinitis)

Definition.—This clinical condition differs from the seasonal type in its specific causes and in the fact that the attacks are not regularly seasonal, but may be continuous or paroxysmal throughout the year. The pathogenesis, functional pathology, symptoms, complications, diagnosis, and diagnostic technic of the seasonal type apply also to this type.

Etiology.—The most important excitants are:

1. Absorbed by inhalation:
   (*a*) Animal danders: Horse, cat, dog, rabbit, goat, cow, guinea-pig, chicken, goose, duck.
   (*b*) Vegetable powders: Orris, rice, corn, wheat, seed of cotton, kapok, flax, dust of hay and straw (not pollen).
   (*c*) House dust.
2. Absorbed by ingestion:
   (*a*) Foods: Milk, egg, fish, shellfish, nuts, chocolate, coffee, buckwheat, celery, bean.
   (*b*) Drugs: Quinin, aspirin, ipecac, senna, iodin, morphin.

When the attack is precipitated by ingestion of the atopen, the coryzal symptoms are usually but the minor part of a general reaction with urticaria, erythema, angioneurotic edema, asthma, and gastro-intestinal disturbance.

The air-borne substances absorbed by inhalation are the actual causes in nearly all instances. They are encountered most frequently in the home, but often at work, or casually. The materials from which pillows, mattresses, quilts, and upholstered furniture are made are numerous and varied: rabbit hair and goat or sheep wool are often found; the feathers of chicken, goose, and duck are, of course, commonly used. The unrefined cotton and kapok used in bedding contain particles of the seeds, and are particularly active in specifically sensitive cases. Orris root, rice powder, and cornstarch are frequent ingredients of cosmetic powders. Cereal flour acts rarely after ingestion, usually by inhalation, and is, therefore, a more common cause of the disturbance among cooks and bakers. House dust is probably the commonest specific agent. The irritant in this seems to be different from all the known substances and as yet has not been identified. The dust of hay or straw is distinct and bears no relation to their respective pollens. It is an etiological factor among farmers and those who sleep on bedding made of grass and straw.

Treatment.—The diagnostic tests are carried out by the scratch or intradermal methods used for seasonal hay-fever. It is particularly important in this type, however, to determine not only that an individual reacts to the test and that the reaction can be verified at will, but also that the individual has actually come in contact with the reacting substance and that it is truly the exciting cause. In other words, one must differentiate between *actual* and *potential* excitants.

The therapeutic principle best applied to the management of these cases is *strict avoidance of all contact with the actual excitants.* If the reaction is to feathers all chance of contact with feathers must be removed. Particular attention must be paid to cleanliness, and the home should be kept as free from dust as possible. At times, change of occupation is required. Foods, if causative agents, must be eliminated from the diet. When contact cannot be avoided, treatment by injection may be employed. The principles of treatment and the procedures are the same as those outlined above for seasonal hay-fever. The disadvantage of this form of treatment lies in the fact that since any immunization is more or less temporary it must be continued for a long time.

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the onset of the primary condition. In the absence of these more obvious causes, the disease is generally seen after middle life.

The *hereditary character* of emphysema has been much discussed. There is some evidence that certain individuals are born with weak elastic tissue and a consequent tendency to early distention of the lungs. Occasionally the condition develops even in young children without obvious obstructive cause. There are numerous examples of the occurrence of emphysema in several members of the same family; and among individuals engaged in the same predisposing occupation there is a great difference in the degree of resulting emphysema. It is safe to assume that there is a considerable individual variation in the elastic quality of the lungs and that some lungs are more resistant to stretching from obstructive causes and can better tolerate such factors as strenuous exercise which tend to cause emphysema.

Another possible cause of distention should be mentioned. Because of the negative pressure in the pleural spaces the lungs tend to adapt themselves to the size of the thorax. In 1858 Freund advanced the theory that at times emphysema may be the result of a primary disease of the costal cartilages which causes hyperplasia, premature ossification, and enlargement of the thorax. It is true that in advanced emphysema there are usually marked changes in the costal cartilages. The difficulty comes in deciding whether distention of the lungs or disease of the cartilages is primary. Freund's theory naturally led him to suggest, as a therapeutic measure, the surgical removal of portions of the ribs to decrease the size of the thorax. While this interesting conception of Freund has never been definitely disproved, the surgical treatment has usually resulted only in disappointment.

Morbid Anatomy.—The essential lesion in emphysema is distention of the alveoli. In the more advanced stages there is rupture of the walls and fusion of several alveoli into one large air sac. Large blebs may be found on the surface of the lung. Upon opening the chest the lungs appear to be larger than normal. They usually collapse slightly, but may remain distended. They are pallid and seem to contain little anthracotic pigment. Pallor and distention are often more marked at the apices and at the sternal margins. The lungs have a feathery consistency and pit on pressure. Microscopically, the air sacs are greatly distended. Changes in the pulmonary vessels are evidenced by all stages of narrowing, obliteration, and rupture, but there is a disappearance of the capillary network before the air sacs atrophy completely. The epithelium of the alveoli undergoes fatty changes. In the bronchi there are evidences of chronic inflammation, and there is peribronchial fibrosis. Bronchiectases may be seen, but are not common. The right heart is often dilated and hypertrophied, the tricuspid orifice being enlarged. The pulmonary arteries suffer atheromatous change.

Morbid Physiology.—*Functional Pathology.*—The extensive anatomical changes of hypertrophic emphysema interfere seriously with the exchange of gases in the lungs. In advanced stages the oxygen saturation of the arterial blood may be diminished from the normal of about 95 per cent. to 90 to 85 per cent. or less, even during rest. During exertion the saturation may be even more greatly diminished. There is interference also with the passage of CO_2 from the lungs and a consequent marked increase in the CO_2 tension in both arterial and venous blood. Several factors contribute to this disturbance of function. The destruction of air spaces with the

diminution of alveolar surface may be of fundamental importance; and the degenerative changes in the remaining alveoli may interfere with diffusion of gases. In emphysema the residual air (the amount of air remaining in the lungs after the deepest possible expiration) is increased, so that the air column through which diffusion of gases must take place is greater than normal. Added to this there is comparative stiffness of the lungs and lack of the churning motion which aids rapid diffusion of gases in normal respiration. The vital capacity of the lungs is diminished in the advanced disease to less than half the normal. There is some evidence that in emphysema the volume of the dead space is increased. The minute volume and the rate of respiration are usually slightly greater, the depth of each respiration somewhat less than normal. Both the relatively shallow breathing and the increase in dead space render each breath less effective and add to the difficulty. All of these factors tend to prevent proper exchange of gases when the patient is at rest, while during exercise their effect becomes more evident. The oxygen saturation of the arterial blood decreases rapidly and CO_2 accumulates. In spite of this the volume of breathing does not increase as much as in normal individuals, no doubt, because of the diminution in the vital capacity and the mechanical limitations of the emphysematous lung. This inability is well demonstrated when an emphysematous patient breathes a 7 per cent. mixture of CO_2 and air. With this powerful respiratory stimulus, a normal individual may increase the volume of breathing six to seven times; a patient with advanced emphysema, on the other hand, may not more than double respiration even when higher percentages of CO_2 are employed. The limitations of breathing which occur in comparatively uncomplicated emphysema may be greatly augmented when there is insufficiency of the right heart. This is a usual accompaniment of advanced emphysema and adds to the distress.

Symptoms.—The onset of emphysema is insidious and the lesions may be well advanced before symptoms become apparent. The first evidence is puffiness and shortness of breath on exertion with, perhaps, moderate cyanosis. In winter there may be persistent bronchitis with an increase of dyspnea. As time goes on, bronchitis becomes more severe, breathlessness may result from slighter exertion, and cyanosis may occasionally become extreme and out of all proportion to the degree of dyspnea or the other symptoms. In no condition, except congenital heart disease, is there such marked cyanosis in ambulatory patients. During the course of emphysema attacks of acute bronchitis in association with the advancing emphysema may simulate asthma. Throughout the early stages of the disease the patient is much more comfortable in summer, but as the process advances there is troublesome bronchitis with a chronic cough in both winter and summer. Sooner or later the symptoms of cardiac distress complicate the picture. As the heart becomes insufficient dyspnea increases, orthopnea develops with edema of the extremities and abdominal symptoms. In the end evidences of chronic cardiac decompensation usually dominate the syndrome. Death most often results from cardiac incompetency, sometimes with sudden dilatation and extraordinary cyanosis. Less often it is due to intercurrent pneumonia.

Physical Signs.—Chronic hypertrophic emphysema may usually be recognized by inspection. The breathing is more rapid and shallow than normal. Even in the early stages there may be moderate cyanosis of the

lips or lobes of the ears which increases with slight exertion. The appearance of the chest is characteristic; the marked increase in the anteroposterior diameter gives to the thorax a barrel shape. There is an upper dorsal kyphosis. The chest is held in permanent inspiration, so that the shoulders appear elevated and the neck shortened. The intercostal spaces are widened. The sternum and intercostal cartilages are prominent. The costal angles become obtuse and in extreme degrees of the disease are almost straight. There are often small venules along the line of attachment of the diaphragm. The apical impulse of the heart cannot be seen, but there is usually marked pulsation in the epigastrium. During inspiration the chest is elevated as one piece, and there is little or no measurable expansion.

Upon *palpation*, the tactile fremitus is feeble, but not lacking. The cardiac apex can usually not be felt. To *percussion* there is an increased resonance, sometimes almost a tympany. The limits of lung resonance are extended in extreme cases to the costal margin. The heart dulness may be obliterated and the areas of hepatic and splenic dulness greatly diminished or lost. Upon *auscultation* the breath sounds are feeble and are often obscured by the râles of bronchitis. Expiration is prolonged and may be four times the length of inspiration. Harsh rhonchi may be heard. Heart sounds are feeble and a systolic murmur of tricuspid regurgitation is audible over the sternum. There may be an accentuation of the second pulmonic sound. The action of the heart is often perpetually irregular. Emphysema in its later stages is one of the frequent causes of auricular fibrillation.

Treatment.—Emphysema is a progressive disease, the rapidity of its progress depending upon the stress to which the damaged lungs are subjected and particularly upon the occurrence of bronchitis. The chief purpose of treatment must be to prevent bronchitis. Whenever possible, the patient should live in an equable, mild climate during the late fall and winter and remain until the spring is well advanced. Unfortunately, such care is rarely possible, and to the vast majority of patients who must remain at work during the winter months, advice must be given concerning the avoidance of sudden chilling and wetting. Clothing should be warm, but so adjusted as to prevent perspiration within doors or chilling without. Sudden changes in temperature involved in going out-doors from an overheated room on a cold winter day are particularly dangerous. The feet should be carefully protected against wet. Dusty occupations, wind instrument playing, and work involving heavy lifting or severe prolonged exertion should be avoided. When the disease is far advanced, with cardiac insufficiency, the treatment can only be palliative and is not different from that for other forms of cardiac decompensation. Inhalation of oxygen may give temporary relief and often quite strikingly affects the cyanosis. In those extreme cases in which there is sudden dilatation of the heart with deep cyanosis bleeding may be beneficial.

Atrophic emphysema is also known as senile emphysema and is found to a greater or lesser degree in most people of advanced age. It has, in common with the hypertrophic form, a dilatation of the air sacs and rupture of many alveoli. The atrophy of the lung tissue is even greater. In contradistinction to the hypertrophic type, the lungs usually collapse to a small mass when the chest is opened. Anthracotic pigment is often abundant. The condition is usually ascribed to senile atrophy. In certain

instances it may possibly be the result of a protraction of the hypertrophic form. The symptoms may be overlooked, but there is usually dyspnea on exertion, chronic cough, and some degree of cyanosis.

Compensatory emphysema results from an overstretching of air-holding portions of the lung when, for some reason, other portions are not functioning. It is always secondary to another process and indicates no primary disease of the dilated portions. It is seen in uninvolved lobes during lobar pneumonia, and occurs with patchy distribution in bronchopneumonia. It may be marked and permanent, with fibrosis of the lung or with pleural adhesions, and less striking in pleuritic effusion and tuberculosis. There are no symptoms and clinically the condition is usually detected by the hyperresonant note which it gives to percussion. In pulmonary tuberculosis and in bronchopneumonia the areas of emphysema may be of sufficient extent to mask the signs of the primary disease.

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DISEASES OF THE PLEURA

PLEURITIS

(*Pleurisy*)

Definition.—Pleurisy or, more correctly, pleuritis is an inflammation of the pleural membrane which may lead to the effusion of coagulable lymph with or without serum or to the formation of pus. Three clinical types of the disease are recognized: (1) acute fibrinous pleurisy—*pleuritis sicca;* (2) pleurisy with effusion—*pleuritis exudativa*—which may, in turn, be subdivided into *pleuritis serosa, pleuritis serofibrinosa,* and *pleuritis purulenta,* according to the type of effusion; and (3) chronic pleurisy with thickening of the pleura or with adhesions—*pleuritis fibrosa.* Other classifications have been based upon the pathogenesis of the disease, but since diagnosis, treatment, and prognosis depend upon the presence or absence of an effusion and the character of the exudate, the classification just outlined seems most practical for the use of the clinician.

History.—Although there is abundant literature dealing with the different phases of pleuritis, especially since empyema was so common during the war, little has been added to our knowledge of the clinical signs of the disease since the time of Laennec, or to the principles of treatment since Bowditch, in 1851, pointed out the value of thoracentesis. Laennec's contribution was a logical result of his invention of the stethoscope which enabled him, in his "Traité de l'auscultation médiate," to lay the foundation for our present knowledge of thoracic diseases.

Study of the bacterial pathogenesis of pleuritis was stimulated in 1918–19 by the epidemic of influenza and its complications, and the literature of that year and the next contains a particularly large number of articles upon this phase of the problems presented by the various clinical forms of pleuritis.

Incidence.—There is little that is significant in the age or sex incidence of pleurisy: it occurs in males and females in the approximate proportion of 2.5 : 1.0; and is most often seen in patients between twenty and forty

years of age. It is of comparatively rare occurrence in infants and in very young children, although empyema is a more frequent sequel of pneumonia in children than in adults. In general, the seasonal incidence corresponds, as one would expect, with that of pneumonia.

Etiology.—Pleuritis is rarely if ever primary, but is secondary to some pre-existing focal infection, usually in the lungs (pneumonia, abscess, or gangrene of the lungs, or pulmonary tuberculosis). It may, however, result from the extension of a disease from some other neighboring organ (pericarditis, malignant ulcer of the esophagus, a subphrenic abscess arising from a gastric or duodenal ulcer, or an hepatic abscess); from a general infection such as septicemia or pyemia; or it may be a metastasis from some distant focal infection (tonsillitis, sinusitis, or appendicitis).

Among other possible causes of pleurisy may be mentioned articular rheumatism, nephritis, and, in very rare instances, gonorrhea. Just how the pleura becomes involved in such diseases is obscure.

Bacteriology.—Although pleurisy is rarely, if ever, spontaneous or primary, the existence of a previous infection cannot in certain cases be demonstrated. This is true of the so-called *primary serofibrinous pleurisy*, which is for the most part tuberculous. In many cases of pleurisy with effusion, signs of pulmonary tuberculosis are readily demonstrable, and in 30 per cent. of the cases the aspirated fluid can be shown by inoscopy to contain *tubercle bacilli*. Lymphocytes are also usually present. In about 75 per cent. (73.7–76.5 per cent.) of the cases of pleurisy with effusion the reaction to the tuberculin test is positive.

In non-tuberculous pleuritis with effusion, which occurs in 20 per cent. or less of all the cases, any one of several varieties of bacteria may play a causative rôle, the *Pneumococcus* and the *Streptococcus* most frequently, and more rarely the *Staphylococcus*, the *Bacillus typhosus*, *Bacillus diphtheriæ*, the *Meningococcus*, and *Friedländer's bacillus*. Even in these, however, bacteria can rarely be demonstrated in the fluid. The *Pneumococcus* is very frequently found in fibrinous or purulent exudates, but seldom in the clear serous effusions. As might be expected, this organism is most commonly found in the empyema which complicates pneumonia, particularly in children. The *Streptococcus*, usually *Streptococcus hemolyticus*, is quite frequently present in the pus during empyema, but very seldom during serofibrinous effusion. It may be recovered during the empyema which follows lobar and bronchopneumonia, abscess, gangrene, and infarction of the lung, bronchiectasis, trauma to the chest wall, and septic infections in other parts of the body.

In the postinfluenzal empyema seen at army hospitals in 1918 the *Streptococcus hemolyticus* predominated. Stone and Swift report that at Fort Riley, Kansas, among the 155 cases of empyema which came to operation the *Streptococcus hemolyticus* was present in 68.4 per cent.; while necropsy cultures showed that this organism occurred in the pleural fluid in 61.9 per cent. of the fatal cases. The *Pneumococcus* alone or associated with the streptococcus or *Bacillus influenzæ* was found in 31 per cent. of the necropsy cultures. The organism least frequently seen was the non-hemolytic streptococcus.

One of the most complete bacteriological studies of empyema made during the influenza epidemic of 1917–18 was that by Brooks and Cecil at Camp Upton. That their report of the relation between the type of

pneumonia and the incidence of empyema is especially significant is shown by the fact that although the incidence of streptococcic and pneumococcic pneumonia was equal, empyema developed in 36 per cent. of the infections with the former organism and in only 11 per cent. of the pneumonic infections. The presence of the same organism in both the sputum and the pleural exudate in the majority of cases examined suggests the importance of the bacteriological examination of the sputum, as an aid to diagnosis, but not as a substitute for the examination of aspirated fluid, which is the only certain diagnostic measure.

In marked contrast to the relative incidence of empyema in streptococcic and pneumococcic pneumonia during influenza epidemics is the incidence during non-influenzal periods when the ratio appears to be reversed. Thus Lord, in studying the pus from 137 cases of empyema, found the *Pneumococcus* present in 54—39.4 per cent. of the specimens, the *Streptococcus* in only 28—20.4 per cent.

Among other organisms occasionally present in the fluid of empyema are the *Streptococcus mucosus capsulatus, Friedländer's bacillus*, the typhoid bacillus, the diphtheria bacillus, the *Micrococcus tetragenus*, and the *Bacillus pyocyaneus.*

Morbid Anatomy.—Inflammatory changes involving the pleura may be unilateral or bilateral, and may involve only a small circumscribed area, or may extend over the entire pleural surface of one side. In acute fibrinous pleuritis the membrane loses its lustre, becomes roughened because of deposition of fibrin, and is more vascular than normal. Small hemorrhages into the pleura are quite frequently seen in the pleurisy complicating influenzal bronchopneumonia. Proliferation and detachment of the endothelial cells of the pleura occur, with increase of the subendothelial connective tissue and leukocytic infiltration of the inflamed parts. In some instances the fibrin forms a very thin membrane; in others, a thick creamy layer. Fibrinous pleuritis may leave behind little or no evidence of its presence; or the parietal and the visceral pleura may become bound together by adhesions which in some instances are so dense that they entirely obliterate the pleural cavity.

In serofibrinous pleurisy, in which in addition to the fibrinous exudate there is an exudation of serum from the capillaries, the quantity of the effusion may vary from a small amount to as much as 4 or 5 liters. The fluid is sometimes encysted. The exudate has a specific gravity of 1016 or more; is rich in albumin; often coagulates quickly on standing; contains leukocytes, red blood-corpuscles, and endothelial cells; and chemically it may contain cholesterin, uric acid, and sugar. In most cases it has a light straw color, but it may sometimes be hemorrhagic. In empyema the fluid is turbid or purulent and contains large numbers of polymorphonuclear leukocytes and often large flakes of fibrin.

When the quantity of effusion is large, the lung is compressed. In fact, in extreme cases the lung may be reduced to a small, elongated, flattened, airless mass which lies in the posterior and upper part of the chest approximately between the levels of the third and the sixth dorsal vertebræ. Downward displacement of the diaphragm depresses the liver and the spleen. As the result of the increased intrapleural pressure on the affected side the heart is displaced toward the opposite side, a change which is more marked in left than in right-sided effusions. The heart, however, is displaced as

a whole, and even in extensive effusions on the left side there is no rotation of its apex. The other contents of the mediastinum, such as the great vessels and particularly the trachea, are also displaced.

JOHN PHILLIPS.

ACUTE FIBRINOUS PLEURISY

Etiology.—Acute fibrinous pleurisy may be *primary* or *secondary*. The *primary* form may result from exposure to cold, but there is usually some evidence of previous disease of the respiratory tract.

The *secondary* type is most frequently caused by some disease of the lung—pneumonia, abscess, gangrene, or infarction. The disturbance is often associated with tuberculosis of the lungs or of the bronchial lymph-glands. Pleuritis may be secondary to tonsillitis, to endocarditis, or to an infection in some more remote part of the body.

Symptoms.—Acute fibrinous pleurisy usually has an abrupt onset, which is promptly manifested by a "stitch" or *pain* in the side. Some types of dry pleurisy, however, are not painful. Often there are prodromal symptoms such as cough and expectoration. In some cases the onset of pain is accompanied by a chill. The pain is stabbing or cutting in character; is increased by deep respiration; may be aggravated by change of position, laughter, or coughing; and is usually located in the fifth or sixth intercostal space in the midaxillary line, but may often be referred to the shoulder in apical pleurisy or to the abdomen or lumbar region when the diaphragmatic pleura is involved. Such referred pain may render diagnosis exceedingly difficult by simulating that of certain abdominal diseases.

In *diaphragmatic pleurisy* the *pain* is often referred to the abdomen in the region of the gall-bladder, to a point above and lateral to the umbilicus (*le bouton diaphragmatique* of de Mussey), or to the region of the appendix. The pain may be referred to corresponding areas on the left side of the abdomen, though diaphragmatic pleurisy on the left side is not as common as on the right. There is often superficial tenderness of the skin over areas innervated by the seventh to the tenth spinal nerves or rarely by the tenth to the twelfth. The pain may be referred to the lumbar region, or, when the central tendon of the diaphragm is involved, to the shoulder and neck along the trapezius muscle.

About 75 per cent. of the patients suffer from a *cough* which is usually dry, hacking and suppressed, and which aggravates the pain. The *respiratory* rate is usually increased as the result of the patient's effort to lessen the coughing and pain by limiting the excursion of the lung. *Fever* nearly always develops and the temperature may rise to 102° or 103° F.

Physical Signs.—The patient often shows evidence of distress and lies on the affected side with the shoulder depressed and the upper part of the spine deflected toward that side in order to reduce the expansion of the lung. The *respiratory rate* is so increased that the pulse-respiration ratio may approach that of pneumonia. If there is much fibrinous exudate the *tactile fremitus* is decreased and the expansion of the affected side is limited.

Occasionally there is marked *tenderness of the skin* over the region of the pleurisy and the *friction-rub* may be palpable. The *percussion note* may be unimpaired, but if there is much exudation of fibrin, its resonance may be decreased.

The rubbing together of the roughened surfaces of the pleura produces an audible to-and-fro leathery *friction-rub* synchronous with the respiration except during the early stages of the disease, when *superficial crepitations*—the so-called "pleural crackles"—can be heard. The most common site of the friction-rub is in the midaxillary line in the fifth or sixth interspace. When the pleurisy is near the border of the heart, the friction sound may be synchronous with the movements of the heart. It is then called a *pleuropericardial friction-rub*. Auscultation shows also that during pleurisy the intensity of the breath sounds is less on the affected side, though they still retain their vesicular character.

In one patient seen by the writer there was a *periostitis of the rib* with considerable swelling over the site of the pleurisy. This subsided shortly after the disappearance of the pleurisy.

In the majority of cases the *leukocyte count* varies from 8,000 to 12,000, although in about 40 per cent. of the cases it is above 12,000 and may be as high as 20,000. When the pleurisy is a complication of pneumonia the figure may be still greater.

The progress of acute fibrinous pleurisy varies. The acute stage with fever lasts about ten days, and the entire course of the disease may be about three weeks. When it is more prolonged the pleura often remains considerably thickened, or serofibrinous pleuritis may develop.

Diagnosis.—In most cases the diagnosis of acute fibrinous pleurisy can readily be made from the history of sudden onset of a pain in the side, which is increased by respiration and coughing, and from the presence of a friction-rub. Diaphragmatic pleurisy, however, is often difficult to diagnose. The conditions to be differentiated from fibrinous pleurisy include pericarditis, herpes zoster, pain in the side caused by irritation of the nerves by spondylitis or a mediastinal tumor, rhonchi from bronchitis, acute inflammatory conditions of the abdomen, acute myositis due to focal infections, etc.

The *pericardial friction-rub* is heard best along the left border of the sternum in the third and fourth interspace, is synchronous with the heart movements, and is not influenced by respiration. The best method therefore for differentiating a pleuropericardial from a pericardial friction-rub is to auscultate while the patient inspires as deeply as possible and holds his breath, and again while the patient expires as fully as possible and again holds his breath, in order to compare the character of the friction-rubs in these two phases.

The appearance of the herpetic eruption establishes the diagnosis of *herpes zoster*, but before its development the pain is often confusing. The pain from pressure on the nerves caused by *spondylitis* or a *mediastinal tumor* is often bilateral and usually of long duration. In cases of doubt an *x*-ray picture of the chest and dorsal spine determines the diagnosis. Loud rhonchi or sonorous râles can be distinguished from a pleural friction-rub by their character and by their disappearance on coughing.

In the *differentiation of diaphragmatic pleurisy* from *acute inflammatory conditions in the abdomen*, such as acute appendicitis or acute cholecystitis, the physician is confronted with a baffling problem. If the following points

are considered, however, few mistakes will be made. During diaphragmatic pleurisy: (1) the temperature is higher, especially if pneumonia is also present, than during abdominal inflammation; (2) the pain is increased on deep inspiration, and the respiratory rate is increased; (3) the leukocyte count is usually higher, particularly when there is also pneumonia; (4) other evidences of respiratory infection, such as cough, cyanosis, herpes, rusty expectoration, and signs of consolidation of the lung, may be present; (5) pressure over the site of pain relieves the discomfort, whereas it increases that of an acute abdominal disturbance; (6) nausea and vomiting may be present, but less constantly than during abdominal inflammations.

Prognosis.—The immediate prognosis of primary acute fibrinous pleuritis is good, but the later outcome is not so favorable. Lord states that of 82 patients with primary pleurisy, 18 (30 per cent.) developed tuberculosis. The prognosis of the secondary type depends on that of the underlying disease.

Treatment.—A patient with acute fibrinous pleurisy should be put to bed and given a diet of easily digested foods and should remain in bed for a few days after the temperature has become normal. The bowels should move daily. The most important part of treatment is to relieve pain. In mild cases the local application of a hot-water bottle or of an ice-bag is sufficient; in others, relief is secured by the application of mustard paste; but in the more severe cases it is necessary to strap the chest with adhesive plaster. This should be applied tightly during full expiration and should extend past the middle line both in front and behind; it should not be allowed to remain in place longer than five days. During its removal care should be taken to avoid abrasion of the skin: this is most easily accomplished by the use of benzine. If strapping does not bring relief of the severe pain, a hypodermic injection of *morphin* should be given. It is important in all cases for the physician to keep in mind the possibility of the presence or later development of pulmonary tuberculosis. Therefore, after the disappearance of the pleurisy the patient should be re-examined at stated intervals and subjected to a general hygienic routine of rest, fresh air, extra feeding, and suitable occupation.

John Phillips.

PLEURITIS WITH EFFUSION

(Pleuritis Exudativa)

Etiology.—Although it is customary to classify pleurisy with effusion as primary or secondary, it is doubtful whether the disturbance is ever primary, even if the site of other infection cannot be discovered. The majority of cases, as has been stated, are tuberculous, but any type of infection may attack the pleura by direct extension or by metastatic conveyance of the organism from a distant focus.

Symptoms.—Usually serofibrinous pleurisy sets in abruptly with the signs previously described as manifestations of acute fibrinous pleuritis. After a few days the pain decreases as the inflamed pleural surfaces become

separated by the fluid. With the appearance of the effusion a dyspnea develops which increases as the quantity of fluid increases.

The *general symptoms* may be quite pronounced. The *temperature* seldom rises above 102° or 103° F., although occasionally it may reach 104° F. Except for moderate morning remissions, the fever persists until accumulation of the fluid stops; the temperature then falls by lysis. *Chills* followed by sweating may occasionally occur. *Digestive disturbances*, such as anorexia, nausea, and vomiting, are sometimes present. If the attack is prolonged there may be considerable loss of weight and strength.

The *dyspnea* is at times very distressing, especially if the fluid accumulates quickly. On the other hand, it is sometimes astonishing to find but little disturbance of breathing when the pleural effusion is large; this can probably be accounted for by the slow accumulation of fluid which permits time for compensation by the opposite lung. When the effusion is moderate in amount the pulse rate increases to over 100 per minute.

There are cases in which none of these symptoms develops, and the only subjective evidence of trouble is that the patient does not feel quite normal.

Inspection.—The *posture* of the patient is significant. He usually lies on the affected side in order to permit freer expansion of the lung on the healthy side. When the quantity of effusion is large he may assume a sitting posture. The mobility of the affected side is lessened, the degree of immobility depending on the amount of the effusion. The scapula on the diseased side is higher than the other, and the spine curves toward the diseased side. If the effusion is massive the intercostal spaces may be obliterated and the volume of the diseased side of the chest consequently increased. In rare instances there is a slight edema of the chest wall. Litten's diaphragm phenomenon is absent. The apex-beat of the heart is displaced toward the healthy side and in right-sided effusions may be as high as the fourth interspace in the midaxillary line. In left-sided effusions a pulsation may be seen to the right of the sternum; this is not due to the apex-beat, but to movements of the right ventricle. The veins of the neck may be distended.

Palpation enables the physician to confirm the results of inspection, particularly as to the comparative immobility of the affected side and the position of the apex-beat. When the effusion is very abundant the trachea may be pushed toward the opposite side. The normal outward movement of the costal margin on inspiration is absent on the diseased side. The tactile fremitus is diminished or absent over the site of the effusion, but on account of the proximity of the compressed lung it may be increased above the upper border of the fluid; at a still higher level it may be normal. As a result of the thickening of the pleura the tactile fremitus may not be restored until long after the absorption of the fluid, but it may, on the other hand, be retained if the lung is consolidated or if bands of adhesions bind the lung to the chest wall. When the effusion is on the right side, the lower border of the liver may be displaced downward; when on the left side, the spleen may be displaced.

Percussion over the fluid reveals an increase in the resistance. The percussion note is flat and high pitched. The upper level of the fluid can be determined more readily by light than by heavy percussion. The area of flatness corresponds to the area of absent tactile fremitus, and in cases of right-sided effusion the area of dulness merges with that of the liver;

in left-sided effusion Traube's semilunar space is obliterated. When the effusion is moderate in amount the upper limit of dulness is a curve (Damoiseau's curve—Ellis's line), which extends upward and laterally from the spine with its highest point in the posterior axillary line, from which it curves downward and forward toward the sternum. In some cases the dulness can be shown to be movable when the position of the patient is changed. When the effusion is of moderate amount there is an area of tympany above the level of the fluid—the so-called "Skodaic" resonance—which is most easily demonstrated below the clavicle. This tympanitic note varies in pitch with opening and closing of the mouth (Williams' tracheal tone), during inspiration and expiration (Friedreich's phenomenon), and when the position of the patient is changed (Gerhardt's phenomenon). Strong percussion occasionally elicits a "cracked pot" sound. With massive effusion the area of flatness may extend to the clavicle. In the lower back on the healthy side there is a triangular area of dulness with the base below and the apex slightly above the upper level of the fluid (Grocco's triangle). Various explanations of this phenomenon have been given, but the consensus of opinion is that it is due to displacement of the posterior inferior mediastinum by the fluid. When the effusion is moderate in amount a triangular area of relative resonance with the base above and the apex below (Garland's triangle) can be demonstrated on the diseased side, in the lower back, close to the spine. This is due to the presence of the compressed lung near the spine and is most evident after the patient has coughed and breathed deeply.

Auscultation at the beginning of effusion into the pleural sac sometimes elicits a friction-rub which can be heard near the upper limit of the effusion. During the process of absorption the friction-rub often reappears as soon as the visceral and parietal layers of the pleura come in contact.

In cases of pleurisy with effusion the direct method of auscultation is frequently used in studying the breath and voice sounds. A comparison of the breath sounds on the two sides often shows that on the well side they are exaggerated by a "vicarious emphysema," while over the site of the effusion they may be distant or absent, according to the thickness of the layer of fluid. At times bronchial breathing with bronchophony and râles may be heard over an effusion, especially in children. Bronchial breathing is often heard in the interscapular region over the compressed lung. Sometimes as the fluid is accumulating a peculiar high-pitched nasal quality may characterize the voice sounds near the upper margin of the effusion (egophony). As a rule, however, the vocal resonance is much diminished; indeed, diminished breath and voice sounds are two of the most important physical signs of pleurisy with effusion. As the fluid is absorbed the breath sounds become louder and vesicular in character.

Auscultation of the heart will frequently indicate a change in its position due to the accumulation of fluid in the pleural cavity. This displacement can be recognized by a change in the location of the maximum intensity of the heart sounds. Often a systolic murmur can be heard over the displaced heart. If the lappet of lung over the left cardiac border is involved a pleuropericardial friction-rub may be audible.

Roentgenoscopy.—Roentgenograms often demonstrate small pleural effusions which are not demonstrable by percussion, and are of particular value in locating encapsulated fluid. It is best to expose the plates with the

patient sitting or standing. The fluoroscope offers a ready means of studying the chest in many different positions, and reveals the displacements of the heart and mediastinum particularly well. As a rule, however, it is best to make roentgenograms.

In the majority of cases in which pleural effusion is suspected it is wise to perform an exploratory puncture, not only in order to confirm diagnosis but also to obtain the fluid for chemical, bacteriological, and cytological study. The information thus obtained is of value in indicating the primary focus of infection and in determining the type of the invading organism.

Atypical Forms of Serofibrinous Pleurisy.—Barker describes four atypical forms of serofibrinous pleurisy: (1) diaphragmatic pleurisy; (2) interlobar pleurisy; (3) mediastinal pleurisy; and (4) pleurisy that is part of a polyserositis. These are of especial interest because they present certain difficulties in diagnosis.

Diaphragmatic Pleurisy With Effusion.—In diaphragmatic pleurisy with effusion the fluid accumulates between the lower border of the lungs and the diaphragm. In general, the *symptoms* and *signs* at the onset of the disease are the same as those which accompany the onset of dry diaphragmatic pleurisy. In many cases the referred pain in the hypochondrium, the shoulder, or iliolumbar region is so marked that there is danger of mistaking the condition for an abdominal lesion.

Interlobar Serofibrinous Effusion.—The interlobar form of serofibrinous effusion is caused by adhesions which prevent the escape of fluid into the general pleural cavity. The *characteristic physical signs* include some limitation of expansion on the affected side, a diminution in tactile fremitus, and dulness on percussion over an area which corresponds to an interlobar fissure, while above and below this area there may be normal or skodaic resonance. The breath sounds are distant over the dull area, while above and below they may be normal or bronchial in character and accompanied perhaps by moist râles. As it is often difficult to locate the fluid by exploratory puncture, a long needle should be used and the puncture made in the axillary line over the area of dulness, keeping in mind the site of the anatomical division between the lobes. Roentgenograms are of great value in detecting interlobar effusions. Sometimes an interlobar effusion communicates with a localized effusion in the general pleural cavity, thus giving rise to the "shirt-stud-shaped effusion" described by Sabourin.

Mediastinal Serofibrinous Pleurisy.—In mediastinal serofibrinous pleurisy the fluid collects either anteriorly or posteriorly between the mediastinum and the pulmonary pleura. The patient often complains of intense pain in the region of the sternum on breathing, coughing, or swallowing. The area of mediastinal dulness may be widened and a friction-rub may be heard to the right of the sternum. The diagnosis of this form of pleurisy can be best established by a roentgenogram.

Serofibrinous Pleurisy With Polyserositis.—When serofibrinous pleurisy is part of a polyserositis there will probably be a pericardial or a peritoneal effusion, or both, in addition to the pleuritic effusion. The majority of these cases are tuberculous.

John Phillips.

EMPYEMA

(*Suppurative Pleurisy*)

Etiology.—Empyema is seldom if ever a primary infection, being usually secondary to an acute pneumonic infection of the lung, to pulmonary phthisis, to gangrene or abscess of the lung, to wounds of the chest wall, or to the extension of an infection from the pericardium or abdomen. Empyema may also complicate infectious processes in other parts of the body.

It is obvious that the organism which is the immediate cause of empyema in any individual is identical with that which produces the infection to which the empyema is secondary. It is important that the character of the invading organism be determined early in the disease as it may have an important bearing upon subsequent treatment.

Morbid Anatomy.—During empyema the pleura is grayish-white or yellowish in color and may be greatly thickened. The inflammation may be general or circumscribed with sacculation of the fluid. Interlobar encapsulation of the effusion is not uncommon. If long continued the inflammation may lead to penetration of the soft tissue of an intercostal space with a resultant external discharge of pus (*empyema necessitatis*). In such cases the inflammation may extend to the interstitial tissue of the lung. Pleural suppuration may extend to the abdomen, the pericardium, or the mediastinum, and it may be complicated by endocarditis, cerebral abscess, or thrombosis of the intrathoracic or other vessels. The exudate of pneumococcus empyema contains large flakes of fibrin, that of streptococcus empyema very little fibrin. In empyema following abscess or gangrene of the lung the fluid may be putrid. The specific gravity of empyema fluid varies between 1024 and 1030 or even higher, and the predominating cell is the polymorphonuclear leukocyte. The color of the fluid is usually yellowish, sometimes with a greenish tinge. The consistency may be thin at first, and later, so thick as to render aspiration difficult.

Symptoms.—The symptoms of empyema are those of a severe illness—fever, chills, tachycardia, sweats, rapidly developing pallor, and weakness. As a complication of pneumonia empyema sometimes develops as early as the third day, especially in cases due to streptococcus infection, but it often occurs later in the course of the disease or even after the temperature has become normal. When the resolution or crisis in pneumonia is delayed the possibility of empyema should be seriously considered. The onset of streptococcus empyema is often marked by extreme exhaustion and by profuse sweating, sometimes without chills.

The *temperature* varies from 101° to 103° F., and not infrequently rises to 104° or 105° F. At the onset of pneumococcus empyema there is a sudden rise in both temperature and pulse rate, while in streptococcus empyema the pulse rate remains comparatively slow and the temperature rises. *Dyspnea* may be a troublesome symptom when pneumonia is still present or when the effusion causes pressure.

A *cough* is a frequent symptom in the early stage and may be quite harassing. In a child seen by the writer in 1913 a large empyema on the right side had so displaced and compressed the trachea that the cough had a curious resounding quality, resembling that of the "gander cough" of aneurysm except that it was higher pitched. This disappeared as soon as the fluid was withdrawn.

In empyema of long standing the patient often shows clubbing of the fingers. The number of leukocytes is much increased, the count varying from 15,000 to 50,000 per cubic centimeter and occasionally rising to an even higher figure. There is a relative increase in the number of polymorphonuclear cells.

Physical Signs.—The physical signs are the same as those characteristic of serofibrinous pleurisy. In children there may be a definite bulging of the diseased side with obliteration of the intercostal spaces, distention of the venules, and some edema of the chest wall. In rare instances there is a pulsating bulging of the chest wall (pulsating empyema). *If there is any doubt as to the presence of empyema during pneumonia, an exploratory puncture should be made.* If pus is not obtained by puncture and the diagnosis is still doubtful, a roentgenogram should be taken. This can be readily done by means of a portable *x*-ray outfit without undue disturbance of the patient. The roentgenogram often demonstrates an encapsulated, a mediastinal, or a diaphragmatic empyema which has produced few if any physical signs, but the picture may be misleading, as it does not always demonstrate the fluid that can be found by puncture. As Brooks and Cecil have said, "The use of the Roentgen ray is indispensable in the diagnosis of empyema, but it will not alone keep the lazy clinician out of trouble with the pathologist."

Differential Diagnosis.—With a careful history, a painstaking physical examination, including a leukocyte count, an exploratory puncture, and a roentgenogram of the chest, the diagnosis of serofibrinous or of purulent pleuritis can usually be made without much difficulty. It is necessary to determine not only the presence of fluid but also its character. If the exudate is purulent, it is necessary to find the causative organisms, as the treatment varies according to the type of the invading bacteria; for example, the treatment of a pneumococcus differs from that of a streptococcus infection.

In the differential diagnosis of effusion into the pleural cavity the possibility of one or more of the following conditions must be considered: (1) acute lobar pneumonia; (2) chronic fibrinous pleuritis; (3) tumors of the lungs, of the pleura, and of the mediastinum; (4) pericarditis with effusion; (5) obstruction or compression of a bronchus; (6) pulmonary abscess; (7) pathological conditions below the diaphragm, such as abscess of the liver or subdiaphragmatic abscess.

The chief points to be borne in mind in the differential diagnosis of *pneumonia* are the sudden onset, the initial chill, the high fever, the rapid respiration, and the rust-colored expectoration, as well as the increased tactile fremitus, bronchial breathing, and bronchophony over the consolidated area. Pneumonia does not, however, always manifest these typical signs. Thus, if there is a plugging of the bronchus with mucus or a thick layer of fibrinous exudate over the pleura, the tactile fremitus may be absent and the breath sounds distant. In such cases the percussion sounds have a wooden character and there is an increased resistance to percussion over the fluid. It is also difficult to distinguish pneumonia from effusion when there is high-pitched tubular or amphoric breathing. Displacement of the organs and obliteration of the intercostal spaces is strong evidence of effusion. If there is any doubt, the physician should make an exploratory puncture with a good-sized needle.

Chronic fibrinous pleurisy may cause all the signs of a small or moderate effusion, but in the former there is no displacement of the heart and little or no elevation of temperature. In doubtful cases a fluoroscopic examination of the chest quickly reveals the absence of fluid.

Tumors of the lung or *of the pleura* may impair the resonance and suppress the breath sounds. Absence of fever, loss of weight, and the discovery of a tumor elsewhere, as in the breast, or a history of the previous removal of a tumor, often lead to the diagnosis of a tumor of the lung or pleura. Tumors of the lung can be readily demonstrated by the Roentgen ray. Tumors of the pleura may be accompanied by an effusion which is sometimes bloody and contains a large proportion of endothelial cells. As a rule tumors of the mediastinum can be differentiated from mediastinal pleurisy by means of the *x*-ray.

It may be difficult to distinguish *pericarditis with effusion* from a left-sided pleural effusion. The diagnosis of a pericardial effusion is determined by the characteristic shape of the area of cardiac dulness, the absence of displacement of the heart, intense dyspnea, the pericardial friction-rub, and normal resonance in the axilla between a large area of dulness in front and an area of posterior dulness caused by compression of the lung. The latter usually manifests itself in a small area at the angle of the scapula over which the breath sounds are tubular in character.

Obstruction of a bronchus by a foreign body or compression by a tumor or aneurysm is evidenced at the base of the lung by the absence of tactile fremitus, by impaired resonance, and distant or absent breath sounds, as well as by the "asthmatoid wheeze" described by Chevalier Jackson. The history, the absence of cardiac displacement, and an *x*-ray examination of the chest confirm the diagnosis.

Patients with *subphrenic abscess* or other conditions which push up the diaphragm and compress the lungs may manifest the same signs on inspection, percussion, and auscultation as when there is fluid in the pleural cavity. It is well to remember that pathological conditions below the diaphragm do not impair the outward movements of the costal margin from the median line on inspiration. The importance of the movements of the costal margin in the differentiation of pathological conditions below the diaphragm from those above it has been emphasized by Hoover. Just as in all other conditions which may obscure the diagnosis of pleurisy with effusion, a fluoroscopic examination of the chest and a roentgenogram will aid in establishing the differential diagnosis.

Prognosis.—The prognosis in *serofibrinous pleurisy* is fairly good, although it is naturally less favorable in patients with active pulmonary tuberculosis. Among the 565 cases of pleurisy with effusion collected by Hamann, 167, or 29.7 per cent., developed pulmonary tuberculosis. Unusual sequelæ may develop, as in one of the author's patients, a man twenty years old, who, though showing no signs of active pulmonary tuberculosis, developed tuberculous meningitis during the third week of a pleurisy with effusion.

The prognosis of *empyema* depends on the associated diseases and on the resistance of the individual. It is very frequently fatal in children under two years of age (published reports show a mortality varying from 32 to 78 per cent.). In children more than two years old the death rate is lower (16–26 per cent.). For patients of all ages Moschcowitz gives mortality

figures which vary from 18.9 to 45 per cent. He quotes Evarts Graham's figure for the average mortality in army camps—30.2 per cent. Lord states that of 252 patients in his series, 22.2 per cent. died in the hospital.

The mortality bears a relation not only to age but also to the type of the infection—*Streptococcus hemolyticus* infections being most often fatal. In many cases death should be ascribed to the co-existent pneumonia rather than to the empyema.

A neglected empyema may rupture internally into the lung or bronchus, or externally through the chest wall, and leave a discharging fistula (*empyema necessitatis*). This usually occurs in the second or third interspace in the midclavicular line. More remote results of an untreated empyema may be encountered, such as arthritis, brain abscess, endocarditis, and amyloid changes in the liver, spleen, and kidneys.

Rare instances have been recorded of perforation of an empyema into other thoracic viscera—trachea, esophagus, pericardial cavity, etc. Most remarkable are the perforations of the diaphragm which cause a general peritonitis. In even more unusual cases the pus burrows along the spine and psoas muscle to the iliac fossa, where it simulates a psoas abscess.

Treatment.—Serofibrinous Pleurisy.—In the acute stage of serofibrinous pleurisy the patient should be put to bed, and given a nutritious and easily digested diet with extra milk and cream unless there is nausea and vomiting. The bowels should move regularly every day. If the temperature is high, a sponge-bath, with water at 90° or 95° F., should be given three times a day. The pain, if severe, should be controlled by codein or morphin.

Thoracentesis should be performed and the fluid aspirated: (*a*) when the quantity of the effusion is large enough to displace the heart and mediastinum; (*b*) when the effusion is moderate in amount, but has developed so rapidly that the patient is dyspneic and cyanotic and has tachycardia; and (*c*) when the effusion is moderate, but fails to absorb after two weeks. When necessary, aspiration should be repeated. The site of the puncture should be either in the sixth interspace in the midaxillary line or in the eighth interspace in the scapular line. To facilitate the operation the interspaces can be widened by elevation of the arm. The puncture should be made under local anesthesia with novocain. In introducing the needle the operator should keep close to the upper border of the rib to avoid injuring the intercostal artery. Aspiration should be stopped: (*a*) if the patient complains of oppression in the chest; (*b*) if he feels faint; (*c*) if he complains of severe pain; (*d*) if a paroxysmal cough begins, especially when it is accompanied by expectoration of frothy sputum. In rare instances sudden death occurs during aspiration, probably as the result of a sudden fall in blood-pressure produced by irritation of the pleura. Capps and Lewis observed that death frequently occurred in dogs subjected to irrigation of the pleura. Sudden death has occurred even during an exploratory puncture. Acute edema of the lungs with albuminous expectoration may develop after the tapping, and proves fatal in about 25 per cent. of cases. This condition is best treated by a hypodermic injection of morphin sulphate (gr. $\frac{1}{4}$) and atropin sulphate (gr. 1/100). A hypodermic syringe containing this solution should be prepared before beginning the aspiration. Occasionally pneumothorax may result from rupture of a vesicle of the lung or from carelessness in technic. Subcutaneous emphysema is rare.

The best evidence that the fluid is being absorbed and that the patient is recovering is a steady fall in temperature. During convalescence all patients should be treated like tuberculous subjects, and given rest, a nutritious diet, and plenty of fresh air. If the patient is anemic, iron should be given. Later he should, if possible, choose an occupation and climate most favorable for the prevention of tuberculous infection.

Empyema.—The treatment of empyema varies with the type and virulence of the infection. When the quantity of effusion during *pneumococcus empyema* is small, patients may occasionally recover completely after aspiration alone. Adhesions form early in pneumococcus empyema, so that thoracotomy and costatectomy may be performed in most cases as soon as the diagnosis is made. If, however, a case of empyema is seen early a primary aspiration may be advisable.

In *streptococcus empyema* adhesions form very slowly. Because of this fact and the consequent danger of collapse of the lungs, because of the danger of infection of the blood-stream, and because the patient is usually desperately ill, it is wise to aspirate every other day until the pus is too thick to run through the needle. Thoracotomy with resection of the rib should then be performed. In these cases it is often difficult to secure adequate drainage, as localized pockets are apt to be separated from each other by adhesions. These are less likely to develop if aspiration is so frequent that no great amount of exudate can accumulate. Irrigation of the chest cavity with Dakin's solution has been advocated by some and condemned by others.

In *tuberculous empyema* thoracotomy is seldom wise because of the active disease in the lung itself. Aspiration should be performed frequently enough to render the patient comfortable.

General measures for the improvement of the strength and nutrition of the patient should be employed in all cases of empyema. Fresh air, good food, and the administration of iron to combat the anemia constitute the chief therapeutic measures. Later, in convalescence, it is important to encourage expansion of the lung by deep breathing or by having the patient blow water from one bottle to another.

John Phillips.

CHRONIC PLEURISY

There are two types of chronic pleurisy: (1) chronic pleurisy with effusion; and (2) chronic fibrous pleurisy with adhesions (*pleuritis fibrosa*).

Chronic pleurisy with effusion is comparatively rare and is generally considered to be the result of unsuccessful treatment of the acute condition. It may be very resistant to treatment because the exudate tends to become pocketed by adhesions. Samuel West reports two interesting cases of this type which were finally cured by free incision and drainage. In the first, the pleural cavity had been aspirated thirty-nine times in twelve months; in the second, the duration of the pleurisy was thirteen months.

Chronic dry pleurisy with adhesions may be a sequel of pleurisy with effusion or may follow an acute fibrinous pleurisy. Nearly always, even

after a mild case of pleurisy, the pleura is altered in some degree. After pleurisy with effusion there is left between the two pleural surfaces a certain amount of fibrin which undergoes organization with the formation of adhesions between the lung and the ribs or between the lung and the diaphragm. These adhesions may be very firm and may even become calcified. Subsequent to an empyema that spontaneously drains through the chest wall, there may develop very dense adhesions which limit the expansion of the lung, or sometimes quite extensive pulmonary fibrosis with resultant shrinkage of the lung.

The only subjective symptoms in these chronic cases are pain after severe exertion and a feeling of limited expansion on the affected side of the chest.

Physical Signs.—The affected side is smaller than the healthy side and its expansion is limited, particularly at the base. Litten's diaphragm phenomenon is absent. The spine is curved, and concave toward the diseased side. The shoulder and nipple on the diseased side are lower and the intercostal spaces are narrower than on the healthy side and the outward movement of the costal margin on deep inspiration is limited. Tactile fremitus is diminished, the percussion note is impaired, and the breath sounds are comparatively feeble over the area of pleurisy.

An *x*-ray examination of the chest shows thickening of the pleura, deformities of the diaphragm, and displacement of the heart and mediastinum toward the affected side. Calcified areas of the pleura appear as circular or radiating shadows.

Treatment.—The treatment of chronic pleurisy with adhesions is designed to build up the patient by the usual dietetic and hygienic measures and to improve the breathing capacity by appropriate physical exercises and pulmonary gymnastics. If pulmonary tuberculosis is suspected, the usual routine for tuberculous patients should be instituted.

John Phillips.

CIRCULATORY DISTURBANCES AFFECTING THE PLEURA

The non-infectious conditions which may cause effusion of fluid in any part of the body may operate within the chest. According to the character of the fluid produced—serous fluid, blood, or chyle—these are classified as *hydrothorax, hemothorax,* and *chylothorax.*

Hydrothorax.—Definition.—The term "*hydrothorax*" is used to designate a transudation of serous fluid into the pleural cavities. This is most frequently the result of cardiac or renal disease.

Etiology.—Hydrothorax usually occurs as a manifestation of general anasarca, but it may be the result of some local obstruction of the circulation of the blood or lymph produced by the pressure of a tumor or of an enlarged mediastinal or bronchopulmonary gland. In some cases hydrothorax may be due to cardiac insufficiency without co-existent general anasarca. It may then be bilateral, but more frequently it develops only on the right side, presumably as the result of pressure on the *vena azygos major* by the dilated

right auricle. Fetterolf and Landis suggest that cardiac hydrothorax may be due to pressure on the pulmonary veins by the dilated portions of the heart. Hydrothorax due to renal disease is usually bilateral.

Symptoms.—The only symptom of hydrothorax is dyspnea. Fever and pain, if present, are due to some other cause.

Physical Signs.—The physical signs of hydrothorax are the same as those of pleural effusion. The fluid obtained by puncture shows the general characteristics of a transudate, having a specific gravity below 1015, and containing very little albumin and few cells. It clots slowly and contains only a small amount of fibrin.

Treatment.—The treatment of hydrothorax consists in aspiration of the fluid if the quantity is sufficient to cause marked dyspnea, and in such general measures as are necessary to relieve the underlying condition.

Hemothorax.—Definition.—The term *hemothorax* signifies an accumulation of blood in the pleural cavity. It does not include the accumulations of hemorrhagic fluids which occasionally result from a tuberculous pleurisy, malignant disease of the pleura, hemorrhagic diathesis, or pneumococcus pleuritis.

Etiology.—Hemothorax is usually due to the rupture of an aneurysm, to the erosion of an intercostal vessel by a tumor or necrotic rib, or to trauma. In the World War the condition was often produced by gunshot wounds or other injuries of the chest and lungs.

Symptoms.—The symptoms of hemothorax may be divided into two groups: (1) those due to the pressure of the rapidly accumulating fluid in the pleural cavity—dyspnea and cough; and (2) those due to anemia from loss of blood—faintness, sweating, air hunger, rapid beating of the heart, and coldness of the extremities. After the first day there is some fever. If the lung is wounded, there is usually hemoptysis.

Physical Signs.—The physical signs are those of fluid in the pleural cavity and of secondary anemia. Exploratory puncture reveals not only blood but also some serous fluid, as the presence of free blood always causes the transudation of a certain amount of serum. The coagulability of the blood is below normal, probably because some change in the fibrinogen is caused by contact with the endothelium of the pleura. During absorption the skin may assume a slightly icteric tinge.

Complications.—Infection of the effused blood is the most serious complication. Pneumohemothorax is not uncommon and occasionally develops into pyopneumohemothorax. Sometimes the injury may cause pneumonia, a pulmonary abscess, or gangrene. A generalized streptococcus septicemia or septicopyemia may at times result. The development of either a localized or a generalized infection is indicated by the usual signs—increasing temperature and pulse rate, chills, sweats, and such local symptoms as increase of the exudate and persistent cough.

Diagnosis.—The diagnosis of hemothorax can usually be made from the history and physical signs. When signs of an effusion into one pleural cavity develop within a few hours after injury they are due to hemothorax. An exploratory puncture or a fluoroscopical examination of the chest verifies the diagnosis.

Prognosis.—The prognosis is always serious, the mortality varying from 30 to 50 per cent.

Treatment.—The patient should be kept absolutely at rest. External

wounds should receive the usual surgical care. Immobilization of the involved side with adhesive tape aids in controlling the hemorrhage, but, aside from this, symptomatic treatment is usually employed. If there is distress from pressure, a slow aspiration may be performed. If the hemorrhage is sufficient to cause alarming symptoms, active surgical intervention may be required to stop the bleeding. Transfusion of blood may be a life-saving measure when there has been a large loss of blood or in cases of infection. If the bloody effusion contains pathogenic organisms, free drainage is necessary.

Chylothorax.—Definition.—"*Chylothorax*" is a term applied to an accumulation of milky fluid in the pleural cavity. This fluid may consist of pure chyle or of a chyliform serous effusion containing fat droplets which are not derived from the lymph channels. In certain cases the fluid may be milky in appearance without containing fat droplets. The milkiness in these cases appears to be due to the presence of albuminous bodies, the exact nature of which is uncertain. Blankenhorn, however, in his report of 7 cases of chylous effusion states that he does not believe that definitely milky fluids have ever been found "the turbidity of which was not due to the presence of emulsified fat derived from the chyle."

Incidence.—Chylothorax is of infrequent occurrence. Rotmann in 1896 succeeded in collecting 49 cases from the literature, and comparatively few cases have been reported since that date.

Etiology.—The presence of *true* chylous fluid in the pleural cavity is due to some injury or obstruction of the thoracic duct by trauma, by a new growth in the pleura, by enlarged glands, or by parasites. When the effusion is chyliform the pleural exudate may be due to any of the causes of a serous exudate, the chylous appearance being produced by fat droplets which have escaped from the disintegrating endothelial and leukocytic cells.

Symptoms and Physical Signs.—The symptoms and physical signs are those of a pleural effusion. The nature of the fluid can be determined only by puncture. In true chylothorax the percentage of fat in the fluid may be as high as 10 per cent.; and a thick cream forms on the surface of the effusion.

Prognosis.—The prognosis depends chiefly upon the underlying disease which is usually of a grave nature. The danger from the primary cause is increased by the pressure of the pleural exudate and by the depletion of the chyle reserve. Of the 22 patients in Rotmann's series, only 4 recovered. Slight lesions of the thoracic duct may heal and the duct remain patent.

Treatment.—The only specific treatment of chylothorax consists in repeated aspiration to relieve the symptoms of pressure. Strapping the affected side may aid by diminishing the respiratory movements and thus stabilizing the pressure. Surgical intervention is rarely of value, although Helferich reports recovery in one case after thoracotomy.

John Phillips.

PNEUMOTHORAX

Definition.—Pneumothorax is a condition characterized by the presence of atmospheric air or of gas in the pleural cavity. Air is rarely present

alone, but is generally associated with a serous effusion (hydropneumothorax) or a purulent effusion (pyopneumothorax).

Various terms are employed to describe the manner in which the air or gas enters the pleural cavity. Thus, when air enters through the chest wall as, for example, after a pleural tapping, the condition is called *external pneumothorax;* when gas enters the pleural cavity as the result of a rupture of the lung *internal pneumothorax* is the term employed. The condition in which the perforation in the wall of the pleural cavity is patent during both inspiration and expiration is known as *open pneumothorax;* that in which the opening is closed during both inspiration and expiration, *closed pneumothorax.* When the perforation is patent during inspiration but wholly or partially closed during expiration the condition is called *valvular pneumothorax.*

History.—Although Hippocrates noted the succussion splash he failed to distinguish between empyema and pneumothorax. Hewson (1739–74) observed the presence of air in the pleural cavity, and in 1803 Itard recognized the relation of pneumothorax to tuberculosis. In 1819 Laennec gave such a thorough description of the symptoms and physical signs of pneumothorax that little has been added up to the present time. Foralini in 1895 suggested the use of artificial pneumothorax in the treatment of tuberculosis and since then there has been increased interest in the subject.

Etiology.—In about 80 per cent. of the cases pneumothorax is due to pulmonary tuberculosis, although it may follow pulmonary gangrene or abscesses, bronchiectasis, pneumonia, pulmonary infarction and pulmonary emphysema, or may be caused mechanically by perforating wounds of the chest or by thoracentesis. Among extrapleural causes may be mentioned subphrenic abscess, perforating ulcer of the stomach or esophagus, and caries of the rib or sternum. In rare instances pneumothorax is associated with tumors of the lung and echinococcus disease. Pneumothorax due to tuberculosis occurs in males about four times as frequently as in females.

Morbid Physiology.—Normally the elastic tension of the lungs produces a negative pressure within the pleural cavity which is greater during inspiration than during expiration. In 36 observations Aron found that the maximum pressure during quiet inspiration was −5.09 mm. of Hg and the minimum for quiet expiration −2.54 mm. of Hg. Because of this negative pressure the admission of air into the pleural cavity on one side causes the lung on that side to retract and the heart and mediastinum to be displaced toward the healthy side where the pleura is still under negative pressure. In open pneumothorax the external pressure is equal to the internal pressure, and consequently respiration is ineffective. In closed pneumothorax the internal pressure is increased, particularly as soon as effusion occurs. Asphyxia may be caused by either open or closed pneumothorax, but more frequently by the former. In valvular pneumothorax the air enters the pleural cavity during inspiration, but cannot escape during expiration, and in consequence the intrapleural tension becomes greatly increased and dangerously interferes with the circulation. Lord reports that in one case of valvular pneumothorax the average intrapleural pressure was +7.93 mm. of Hg at the height of inspiration and +10.48 mm. of Hg during expiration. In these cases there is a compensatory emphysema of the healthy lung.

Symptoms.—The onset of pneumothorax is sudden and without any apparent cause. The patient is suddenly seized with a sharp, stabbing, tearing *pain* in the side of the chest "as if something had suddenly given

way." The pain is usually felt in the midaxillary region but may be referred to the scapula or beneath the clavicle, or may radiate around the chest. As a rule, it is of short duration. Accompanying the pain is a *shortness of breath* which steadily increases. The patient is usually found sitting up in bed in great distress with a pale face, bathed in perspiration, and with cold extremities. The *mental distress* is extreme, as the patient feels that he is about to die. The dyspnea may be so severe that it is necessary to insert a needle into the side in order to allow the air to escape; if the air reaccumulates rapidly, it may be necessary to repeat the puncture several times. Some patients die in spite of repeated tappings; in others the dyspnea gradually becomes less severe, and the urgency of the symptoms disappears. The onset may at times be so insidious that the first indication of pneumothorax is the succussion splash.

Physical Signs.—On inspection, the affected side is seen to be greatly distended, the shoulder raised, and the intercostal spaces widened. The respiratory excursion is very slight, with no outward movement of the costal margin on deep inspiration. The superficial veins are sometimes dilated and there may be slight general edema of the whole side of the chest. The heart is displaced toward the unaffected side, and its impulse may be seen in the new position. The patient usually assumes a sitting or half-sitting position. In Garde's remarkable case the knee-chest position was assumed.

Palpation confirms the results of inspection. Tactile fremitus on the affected side, if felt at all, is indistinct; in the majority of cases it is entirely absent. In right-sided pneumothorax the right lobe of the liver may be displaced downward. The larynx and trachea may be shifted toward the healthy side. If an effusion has developed, a splashing sound may be audible when the patient is shaken (Hippocratic succussion splash). This can sometimes be heard at quite a distance and can often be voluntarily produced by the patient.

The *percussion note* varies with the tension of the gas in the pleural cavity, the position of the retracted lung, the presence of adhesions, the character of the pneumothorax—whether open or closed—and the amount of fluid in the pleural cavity. It may vary in quality from tympany to dulness. Usually the note is hyperresonant, and if the pneumothorax is large the hyperresonance may extend beyond the limits of the normal lung. Occasionally a "cracked-pot" sound may be obtained, which is caused either by the proximity of a pulmonary cavity to the chest wall or by the communication of a large open fistula with the pleural cavity. If fluid or pus is present percussion over the lower portion of the pleural cavity elicits a dull or flat tone, and the dull area is demarcated from the resonant area by a horizontal line, which is in contrast to the curved upper limit of dulness in pleural effusion without air.

In most cases *auscultation* shows the breath sounds to be greatly diminished on the affected side and exaggerated on the healthy side. This contrast, and the hyperresonant percussion note, are usually the first signs that lead to suspicion of pneumothorax. If an open fistula exists, the breath sounds may be amphoric in character, and a gurgling sound (the so-called "water whistle" murmur) may be produced. The whispered and spoken voice sounds are decreased. Often at the end of inspiration there is a peculiar metallic tinkle, comparable to that produced by striking a glass

vessel with a pin. This is thought to be due to the bursting of bubbles of air which have risen to the surface of the fluid from a submerged fistula, or to the falling of drops from the walls of the cavity to the surface of the fluid below. The coin sound (*bruit d' airain*) produced by the tapping of one coin with another on the anterior part of the chest while the examiner listens posteriorly is very characteristic. It is a ringing metallic sound quite unlike the normal resonance of the healthy lung.

Gas Analysis.—In experiments on dogs Emerson found that when air is introduced into the pleural cavity the nitrogen content remains constant, but the oxygen content quickly diminishes, and there is a rapid accumulation of carbon dioxid. If the amount of oxygen remains normal, the presence of an open fistula is suggested. Air is quite rapidly absorbed from the normal pleural cavity—in most cases within about a week—but when the pleura is diseased the process may take several weeks.

A *Roentgen-ray examination* of the chest should be made when pneumothorax is suspected. The characteristic roentgenographic signs of pneumothorax are abnormal clearness of the affected side, absence of the normal lung markings, retraction of the lung, displacement of the heart and mediastinum, depression of the diaphragm, and the horizontal level of the fluid. If the patient is shaken, waves in the fluid may be observed. A fluoroscopical examination may show the so-called "paradoxical contraction of the diaphragm," the diaphragm moving upward on inspiration and downward on expiration.

Diagnosis.—The recognition of pneumothorax, as a rule, presents no great difficulty if the possibility of its existence has occurred to the physician. The history of a sudden onset of pain and dyspnea, immobility of the affected side, with diminished tactile fremitus, hyperresonance, decrease of the breath sounds, displacement of the heart and mediastinum, and the presence of the coin sound all indicate pneumothorax.

In the *differential diagnosis* one must consider: (1) the presence of a large pulmonary cavity; (2) subphrenic pyopneumothorax; (3) diaphragmatic hernia; (4) gaseous distention of the stomach; and (5) pleurisy with effusion.

Pulmonary cavities are seldom large enough to make their differentiation from pneumothorax difficult. An enormous cavity might be mistaken for pneumothorax, for the percussion and auscultatory signs could be the same; but the onset of a cavity is not sudden, and there is no displacement of the heart or mediastinum. A roentgenogram will also demonstrate that the diaphragm is elevated rather than depressed.

The differentiation of *subphrenic pyopneumothorax* may be very difficult. The history will usually indicate the presence of some abdominal lesion such as perforation of a gastric or duodenal ulcer or of the appendix. The liver is depressed and the lower portion of the lung compressed. There may be resonance or tympany above the level of the compressed lung and movable dulness below, with amphoric or diminished respiratory murmur, metallic tinkle, coin sound, and succussion splash. The mobility of the chest is not interfered with as much as in pneumothorax, and the costal margin on the affected side may move outward. The heart is only slightly displaced. Roentgenograms show that the diaphragm is pushed upward, and that there is a relatively clear space in the costophrenic sinus. The pus obtained by puncture often has a fecal odor. In many cases jaundice is present.

Diaphragmatic hernia provides a history of trauma with attacks of colic, nausea, and vomiting. If a barium meal is given, the condition can be readily diagnosed.

Gaseous distention of the stomach can be easily determined by the passage of a stomach-tube or by *x*-ray examination.

In *pleurisy with effusion*, even though there may be amphoric breathing, the succussion splash, metallic tinkle, and coin sound are absent.

To differentiate surely between hydro- and pyopneumothorax, an exploratory puncture is necessary.

Prognosis.—The course and prognosis of pneumothorax depend to a certain extent on the underlying cause. The majority of patients die within the first few days. Of West's 39 patients, 10 died within twenty-four hours, 18 during the first week; and the total mortality for 74 cases was 70 per cent. Death during the first day is due either to circulatory embarrassment or to suffocation from a sudden discharge of the contents of the cavity into the air tubes. When death occurs later it is due to the effusion which follows the pneumothorax. In other cases death is caused by the original disease which is usually tuberculosis. Spontaneous pneumothorax, excepting the suffocative type, is rarely fatal. Fussell and Riesman report only one death among 58 cases.

Treatment.—Absolute rest should be assured and the cough controlled by the administration of morphin. The affected side can be immobilized by strapping, and the patient should be instructed to avoid deep breathing and coughing, if possible.

Patients usually recover from spontaneous valvular pneumothorax if left alone, but when the respiration and the circulation are greatly embarrassed, aspiration should be performed at once to relieve the intrapleural pressure, and repeated as often as necessary. When the condition is not so urgent it is well to avoid aspiration as long as possible to allow the fistula to close, especially in cases of serous effusion, when the aspiration should be delayed for two weeks if possible. The same plan may be followed in the treatment of pyopneumothorax unless the symptoms of sepsis are too severe. If removal of the exudate is indicated, aspiration should be followed by resection of a rib and drainage.

John Phillips.

PARASITICAL INVASIONS OF THE PLEURA

In rare instances the pleura may be invaded by *actinomyces bovis* and by *streptothrix*, which produce very similar clinical and pathological pictures. In *actinomycosis* the pleural infection may be an extension from the neck, the esophagus, or the abdominal cavity. Erosion of the ribs and perforation of the chest wall are common features. The diagnosis can be established by the presence of granules with branching Gram-positive filaments and radially disposed club-shaped eosin-staining bodies. The prognosis is grave. *Treatment* consists in a combination of the internal administration of potassium iodid, and surgical measures.

In *streptothricosis of the pleura* the infection is an extension from the lung. Clinically, the condition resembles tuberculosis. There may be multiple pulmonary abscesses. The presence of thread-like, branching organisms which, to a considerable degree, resist decolorization with acid and alcohol establishes the diagnosis.

Echinococcus disease of the pleura is very rare in this country. The right pleural cavity is more frequently affected. The symptoms often resemble those produced by a slow-growing intrathoracic tumor. Dyspnea increases progressively. Fever is absent but emaciation is quite common. The physical signs are those due to encysted pleural fluid. There may be echinococcus cysts elsewhere in the body. The blood shows eosinophilia. Urticaria is often present. The *treatment* is surgical.

JOHN PHILLIPS.

TUMORS OF THE PLEURA

Tumors of the pleura are comparatively rare. They may be either benign or malignant. Benign tumors are extremely rare, although lipoma, fibroma, osteoma, angioma, and xanthoma of the pleura have been described. The lipomata arise either from the subpleural fatty tissue or from the fatty tissue of the thoracic wall.

Primary malignant tumors—carcinoma, sarcoma, and endothelioma—are of very rare occurrence; metastases from primary new growths in the breast, lungs, stomach, esophagus, or thymus are much more common.

Symptoms and Physical Signs.—The symptoms and physical signs of pleural tumors somewhat resemble those of pleurisy with effusion. As a rule fever is absent. Loss of weight and strength and emaciation are usually marked and there is a progressive secondary anemia. The fluid obtained by tapping may be straw colored, but is not infrequently bloody, and has a specific gravity of less than 1018. It contains a larger proportion of endothelial cells and fewer lymphocytes than the ordinary transudate. The presence in the pleural exudate of rosettes of cells or of cells showing mitosis is thought to be pathognomonic of malignant disease of the pleura.

Prognosis.—The prognosis is bad. The disease, as a rule, terminates fatally within six months, though in some cases death may not ensue for twelve or eighteen months.

Treatment.—The treatment is symptomatic. Aspiration should be performed if the dyspnea is urgent. Morphin should be administered to relieve pain or distress. There is some evidence that life may be prolonged by the use of radium or by deep *x*-ray therapy.

JOHN PHILLIPS.

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Diseases of the Mediastinum

Affections of the mediastinum which should be considered as separate entities distinct from the diseases of certain structures within the mediastinum may be divided into two main groups: (1) those involving the connective tissue of the mediastinum, including acute and chronic mediastinitis, mediastinal abscesses, mediastinal hemorrhage, and mediastinal emphysema; and (2) tumors of the mediastinum.

Mediastinitis.—Simple mediastinitis without suppuration may be associated with pericarditis, pleurisy, pneumonia, or syphilis. The subjective symptoms are fever, pain beneath the sternum, and occasional coughing. Physical examination reveals no very positive changes. Crepitations may be heard along the border of the sternum, and the area of mediastinal dulness may be somewhat increased. The course of the disease is usually comparatively short, but the simple form may become suppurative.

Indurative Mediastinitis.—In some cases acute mediastinitis is followed by a great increase in the fibrous tissue—indurative mediastinitis—with adhesions and compression of the great vessels. Cyanosis, dyspnea, and cough are the prominent symptoms. The superficial veins are enlarged and the mediastinum broadened, as may be shown by the *x*-ray and by percussion. Often a creaking friction-rub may be heard. Sometimes associated adherence of the pericardium causes the development of ascites and swelling of the feet. If the thoracic duct is compressed the ascitic fluid may be chylous.

Suppurative mediastinitis is always a serious disease. It is most commonly associated with tuberculous disease of the lymphatic glands, but may also be the result of injury, such as gunshot wounds, or of ulceration of the esophagus produced by the presence of foreign bodies, such as artificial teeth or coins. It may be due to inflammation of the sternum or of the spine; or may be secondary to an inflammatory condition in the neck, such as a retropharyngeal abscess, or suppuration of the thyroid or thymus, the inflammation spreading from the cellular tissues to the mediastinum. Some cases are due to a general infection, such as erysipelas and pyemia; or mediastinal infection may be an extension from an inflammation of the lungs or pleural cavity. Abscesses of the mediastinum may rupture into the esophagus, pericardium, pleura, lung, trachea. or bronchus. Cases are recorded in which an abscess has ruptured into the arch of the aorta and produced fatal hemorrhage.

The *chief symptoms* of suppurative mediastinitis are fever, which tends to be of the hectic type, sweating, local pains, and a gradually increasing shortness of breath. There may be marked symptoms of pressure. As the disease progresses there is anemia and wasting. The majority of these cases are fatal, though in some instances when the pus makes its way to the surface, there is ultimate recovery. Should the abscess rupture into the trachea or bronchus, a large quantity of pus may be coughed up, or death may speedily result from suffocation.

Tuberculous Mediastinitis.—Tuberculosis may involve any of the groups of the mediastinal glands, but the tracheal and bronchial glands are those most frequently affected. Involvement of the intrathoracic glands usually results from the extension of an infection from the neighboring structures, especially from the lung or the pleura, and occasionally from bone.

The tuberculous process may extend directly from the glands of the neck or along the lymphatics through the diaphragm from those in the abdomen. This condition sometimes follows an acute infection, such as whooping-cough. It is more common in children than in adults. That in children enlargements of the tracheobronchial glands are frequently not tuberculous must, however, be kept in mind, as these glands are always enlarged in acute bronchial infections in children and also in so-called glandular fever. The glands have a tendency to become caseous, then purulent, this being a common origin of chronic abscesses within the mediastinum. They may perforate into the aorta or pulmonary artery and cause fatal hemorrhage; or they may ulcerate into the trachea or into the thoracic duct, and thus sometimes cause acute miliary tuberculosis.

Symptoms.—The symptoms of tuberculous mediastinitis are fever, wasting, anemia, night-sweats, loss of appetite, more or less disturbance in breathing which sometimes simulates spasmodic asthma, and coughing, which may be spasmodic and croupy in quality, or may occur in paroxysms resembling those of whooping-cough. If the glands should rupture into the trachea the patient may cough up purulent or caseous material. In some chronic cases even calcareous particles may be expectorated. Physical examination discloses marked dulness over the sternum, particularly when the anterior mediastinal glands are tuberculous. Eustace Smith has described in children a venous hum which is audible at the root of the neck when the head is thrown back. This he attributes to pressure of the enlarged glands on the venous trunks. Whispered bronchophony below the level of the fourth dorsal vertebra, usually more marked on the right side than on the left, suggests enlargement of the bronchial glands (D'Espine's sign). Since these signs are to a certain extent identical with those produced by a small cavity or by certain pleuritic conditions, their significance should be established by stereoscopic roentgenograms of the chest which disclose the presence of enlarged glands.

Treatment.—The treatment of *simple mediastinitis* consists of rest in bed, local applications of heat to the sternum, and the administration of codein or morphin to relieve the cough. If the disease passes into the *chronic* or *indurative* stage and is associated with adherence of the pericardium and cardiac dilatation, digitalis should be given to support the heart. In any case the general treatment should be adapted to the underlying condition. Thus, if the mediastinitis is syphilitic in origin, antisyphilitic treatment with mercury and potassium iodid should be given. In tuberculous mediastinitis the usual hygienic measures—rest, fresh air, and extra nourishment—are indicated. In chronic suppurative mediastinitis, if the symptoms of pressure are not severe, an expectant policy may be justified, as the pus may burrow toward the surface. If the process is acute, prompt surgical measures may be required. The search for pus is usually difficult, however, and, even if successful, rarely saves the patient's life.

Mediastinal hemorrhage is most frequently due to perforation of the aorta or one of its branches, and is rarely recognized during life. The writer has seen one case of rupture of the descending thoracic aorta in which the symptoms were referred to the abdomen, and resembled those of perforation of a gastric or duodenal ulcer. The patient was in severe shock and died after two hours.

Mediastinal emphysema may occasionally result from inflammations

in the mediastinum, the air gaining access to the mediastinum through a perforation of the trachea or bronchus, or making its way from the neck beneath the deep cervical fascia. In some instances the air may extend through the cellular tissue of the neck or over the front of the chest, and give rise to an extensive subcutaneous emphysema.

True mediastinal emphysema should be differentiated from the so-called *subfascial* or *false mediastinal emphysema* which sometimes results from artificial pneumothorax.

The only *external symptoms* of mediastinal emphysema are subcutaneous emphysema in the neck, and dyspnea if there is great pressure. The *physical signs* are a high and tympanitic percussion note over the mediastinum, and in some cases obliteration of the heart dulness. Auscultation may elicit crepitation and distant heart sounds, or the latter may be inaudible.

Treatment should be directed to the underlying cause of the emphysema.

Tumors of the mediastinum may be primary or secondary, malignant or benign. Benign tumors are comparatively rare, although fibroma, lipoma, chondroma, myoma, intrathoracic adenoma or cystadenoma of the thyroid, simple echinococcus, and dermoid cysts have been described.

Different forms of *sarcoma* comprise the group of primary tumors which develop most frequently in the mediastinum. They are usually primary growths originating in the loose connective tissue of the mediastinum, in the peribronchial and mediastinal lymph-nodes, and in the thymus. Secondary sarcoma of the mediastinum may follow sarcoma in the arm, leg, or other parts of the body, while, on the other hand, primary mediastinal sarcoma may be followed by the development of metastatic nodules in the liver, spleen, and kidneys.

Mediastinal carcinoma is usually secondary to carcinoma elsewhere (for instance, in the breast or gastro-intestinal tract), but in rare cases is primary, the growth arising in the epithelium of the esophagus, the trachea, the bronchi, the thymus, or in a misplaced or accessory thyroid gland.

The majority of tumors of the mediastinum develop in patients between thirty and fifty years of age.

Symptoms.—In considering the symptoms and physical signs caused by mediastinal tumors it is important to have in mind the anatomical structures within the mediastinum which may be compressed. These include the superior and inferior vena cava and vena azygos major, the aorta and its branches, the pulmonary artery, the trachea and bronchi, the esophagus, the thoracic duct, the heart and pericardium, the vagus, sympathetic and phrenic nerves, the vertebral column, and the sternum.

The outstanding symptoms are pain, disturbance in respiration, coughing, and dysphagia. The *pain*, which is usually quite constant, may vary from a feeling of pressure to a burning sensation with periods of acute exacerbation. The *respiratory disturbances* may vary from a steady progressive shortness of breath to a well-defined inspiratory stridor which is often accompanied by wheezing. Sometimes, especially in intrathoracic goiter, there may be very severe attacks of suffocation because of the incarceration of the goiter in the superior strait. Cyanosis is often present. Just as when there is profuse pleuritic effusion, the patients are often obliged to maintain the sitting posture or, at times, the knee-chest position. An enormous mediastinal lipoma described by Leopold weighed 17 pounds, 6 ounces (7.9 kg.). In a case recently seen by the author a sarcoma, which

probably originated in the mediastinum and entirely filled the right thoracic space, weighed 15 pounds (6.8 kg.). The *cough* may be paroxysmal, but in many cases is the expression of a constant effort on the part of the patient to relieve the feeling of obstruction. It frequently has a curious resounding character—the so-called "gander" cough. The expectoration, as a rule, is small in quantity and consists of thin, viscid mucus; at times, however, it is profuse, mucopurulent, or purulent, and if the tumor is a dermoid cyst may contain hairs or other characteristic structures. The expectoration is often streaked with blood. If the tumor invades the trachea there may be profuse hemoptysis.

The *dysphagia* is usually due to the pressure of the tumor upon the esophagus; and as the obstruction progresses a pouch-like dilatation of the esophagus may form and cause regurgitation of food.

In addition to the above symptoms, *cardiac palpitation* and other cardiac disturbances may be caused by pressure on the heart; there may be anginal attacks and inequalities in the radial or the carotid pulses. Pressure from the tumor may produce an erosion of the aorta with resultant hemorrhage. Venous obstruction may cause an extensive venous thrombosis accompanied by the usual subjective symptoms of enormous distention of the veins of the upper part of the chest and neck, particularly in the rare cases of thrombosis of the superior vena cava. The larynx may be fixed so that it no longer ascends and descends with respiration and deglutition. The heart may be displaced.

The principal signs of the presence of a mediastinal tumor elicited by a *physical examination* are a bulging of the chest wall and distention of the veins. Sometimes there may be an abnormal pulsation, and when the tumor extends above the upper border of the manubrium sterni it can be both seen and palpated. There may be cyanosis and swelling of the face, neck, and upper extremities.

In general, the physical signs revealed by percussion, auscultation, or palpation obviously depend upon the position, size, and distention of the tumor. *Percussion* reveals a widening of the mediastinal area of dulness; and if there is obstruction of a bronchus or an accompanying pleural effusion this dulness or flatness may be observed on the affected side of the chest. The *auscultatory signs* vary a great deal in different cases. When a tumor is situated in the superior mediastinum the quality of the breath sounds may be intensely tubular or amphoric. If the trachea is partially obstructed the breath sounds may be feeble throughout both sides of the chest, but accompanied by a stridor. At times a pleuritic friction-rub may be heard in the region of the tumor. If fluid is present in the pleural cavity the usual signs of pleurisy with effusion are present.

Differential Diagnosis.—In the differential diagnosis a careful history and physical examination are of prime importance. Of particular significance is the presence of tumors elsewhere or the history of a previous operation for tumor. A *fluoroscopic examination* is of value in the final establishment of the diagnosis provided the observations are carefully correlated with the physical findings and the history. The mediastinal space should be viewed from different angles and the position of the trachea should be carefully observed, as any abnormal variation indicates a displacement of the mediastinal contents. The various types of tumor give fairly characteristic shadows which may be distinguished by the trained observer.

It may be difficult to distinguish a mediastinal abscess from a tumor, but when the mediastinal abscess has developed from disease of the vertebræ it usually assumes a fusiform shape, gradually tapering off toward the diaphragm. In Hodgkin's disease there are often large, discrete shadows which correspond to the individual glands, and the same is true of leukemia. In the latter case blood examination serves to determine the diagnosis. An esophageal diverticulum can usually be readily distinguished from a tumor by means of a fluoroscopic examination after barium has been given by mouth.

The differentiation between aneurysm of the aorta and tumors of the mediastinum is of special importance. A significant finding which practically establishes the diagnosis of aneurysm is the maintenance of the normal form and position of the arch of the aorta.

A *laryngoscopic examination* often gives the first clue to the presence of mediastinal pressure by disclosing a paralysis of one of the vocal cords or evidences of compression of the trachea.

Laboratory examinations may also be of service. For instance, when a mediastinal tumor is associated with enlargement of the glands in the supraclavicular space, it is very easy to remove one of these glands for histological examination. This permits certainty of diagnosis. Blood-counts are of value, particularly in cases of leukemia. The examination of the sputum in cases with profuse expectoration or with hemoptysis is of value in differentiating the condition from tuberculosis. The finding of teeth and hair in the sputum serves to clinch the diagnosis of the rare dermoid cysts.

In general, it should be emphasized that the establishment of the diagnosis of a mediastinal tumor should not depend upon any one method, but that every diagnostic measure at our command should be employed, the final diagnosis resting upon the correlation of all the findings.

Treatment.—With the exception of intrathoracic goiters, mediastinal tumors can rarely be removed by operation. Surgical treatment is never of avail for secondary tumors, and the mortality is high among the recorded cases in which the removal of primary tumors has been attempted. *x*-Ray therapy, on the other hand, is of considerable value.

Fibroid tumors occasionally yield to radiation. The growth of carcinomata may be retarded, but as tumors of this type are usually metastatic, even if the mediastinal tumor is controlled, the measure is but palliative, and other metastases will almost certainly develop. On the other hand, the radiation of lymphosarcomata yields quite favorable results; these tumors are reduced in size, and occasionally permanent benefit is secured.

The local involvement of the glands in Hodgkin's disease and in lymphatic leukemia yields readily to radiation, but the improvement is only temporary. In these cases *x*-ray therapy is only a palliative measure.

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Diseases of the Diaphragm

When one considers the important relation of the diaphragm to the function both of respiration and of circulation, and remembers that there is nothing in its structure to protect it from the injuries and diseases to which like tissues elsewhere may be subjected, it is surprising that diseases of this organ have received such slight attention. The apparent neglect may be due in part to the fact that usually the disease process which attacks the diaphragm is part of a systemic disturbance or the disease of a neighboring organ or tissue. Within the past decade, however, interest in pathological conditions of the diaphragm itself has been aroused, in particular by the writings of Hoover. He has emphasized certain facts in regard to the function of the diaphragm, especially in their relation to the physical diagnosis of diseases above and below the diaphragm; and he calls attention to the fact that the movements of the costal margins during inspiration are the resultant of activation of the diaphragm and of the intercostal muscles. Normally because of its arch the diaphragm contracts at a disadvantage and, therefore, the intercostal muscles gain mastery over it, the costal margins moving outward during inspiration. When the arch of the diaphragm is depressed, however, as in emphysema or in pleurisy with effusion, it contracts to greater advantage, and the costal margins are restricted or move toward the median line.

Diaphragmatitis.—Primary inflammation of the diaphragm is rare, but on account of the rich blood and lymphatic supply an infection readily extends to it from neighboring organs, or a generalized infection may become localized. The possibilities of the latter occurrence have been especially studied by MacCallum. The muscle of the diaphragm appears to be a favorite site for the lodgment of trichinæ, a fact which explains the troublesome dyspnea sometimes associated with trichinosis.

The pleural covering of the diaphragm is frequently invaded by the agents which cause any generalized or localized pleurisy (diaphragmatic pleurisy).

Symptoms.—The chief symptoms of diaphragmatitis are dyspnea, a feeling of soreness and a sense of pressure over the lower part of the chest, and pain which is referred to the abdomen and neck, as in diaphragmatic pleurisy. The chief physical signs are absence of Litten's sign, restriction of motion of the lower part of the chest, soreness on pressure, suppression of breath sounds at the base of the lung, and sometimes the presence of superficial râles along the line of attachment of the diaphragm. Fluoroscopic examination of the chest shows that the diaphragm is immobile.

Prognosis.—The prognosis depends on that of the underlying condition.

Treatment.—The patient should be kept at rest. The local application of heat and a binder around the lower part of the chest will relieve the symptoms. If the pain is severe it may be relieved by the administration of acetyl salicylic acid, codein, or morphin.

Spasm of the Diaphragm.—Spasms of the diaphragm may be either tonic or clonic in character, the latter being much more common and much less serious than the former.

The most common form of *clonic spasm* is that known as hiccup.

Clonic spasms with or without hiccup may be associated with diaphragmatic pleurisy or with any acute inflammatory condition within the abdominal cavity. In some cases, however, the source of irritation is in the central nervous system, as in brain tumor, apoplexy, or encephalitis. In many cases the spasms are due to indigestion. They are not infrequent in influenza. In acute abdominal conditions, because of the violent disturbance of the neighboring viscera, such spasms of the diaphragm are often of serious import.

Tonic spasms of the diaphragm are usually symptomatic of a general condition such as epilepsy, tetanus, strychnin poisoning, or eclampsia; they may occur in hydrophobia, and in rare instances have been associated with asthma. The spasm may be short or prolonged, the outstanding symptom, dyspnea, being intensified accordingly. If of long duration and associated with spasm of the intercostal muscles the patient dies of asphyxia.

Treatment.—*Clonic spasms* of the diaphragm may be relieved by inhalations of ammonia, by traction on the tongue, or compression of the chest, by bromids, or, in severe cases, by morphin. Hiccup due to indigestion is best relieved by frequent feedings with milk or with milk and cream, alternating with the administration of alkalis.

Tonic spasms may sometimes be stopped by the application of vigorous counterirritation over the regions of diaphragmatic attachment—the epigastrium, the thoracic walls, the lumbar region. Hot compresses and cupping may prove of value, or electric stimulation of the diaphragmatic areas. The usual antispasmodics, such as chloroform, ether, and bromids, may be employed.

Paralysis of the Diaphragm.—The phrenic nerve in its course or at its origin in the cervical cord may be involved in diphtheria in poliomyelitis, or in inflammatory conditions of the lungs or pleura; it may be contused by injuries or be pressed upon by tumors or by hemorrhages into the cervical portion of the spinal cord, with resulting paralysis of the diaphragm. The paralysis may be unilateral or bilateral, the latter being very serious.

Signs and Symptoms.—Fowler has described the signs and symptoms of paralysis of the diaphragm as follows: (1) Reversal of the respiratory movements of the epigastrium and hypochondria, with recession rather than bulging in these regions during inspiration; (2) absence of the downward movements of the abdominal viscera during inspiration; (3) increased outward movement of the lower ribs during inspiration; (4) dyspnea on exertion or excitement; (5) alteration in the voice and cough; (6) loss of the compressive action of the abdominal muscles on the viscera during defecation; (7) feebleness of expiration and of such reflex expiratory acts as coughing and sneezing; (8) diminution of the total capacity of the thorax as the result of increased arching of the diaphragm. The latter condition, as well as the partial or complete immobility of the diaphragm, can be demonstrated by fluoroscopic examination.

Prognosis.—The prognosis is grave, varying directly with the extent of the paralysis. When the paralysis is complete, fatal asphyxia may follow even the slightest exertion.

Treatment should be directed toward improving the condition to which the paralysis is primarily due. In some cases the local application of electricity may be of value.

Diaphragmatic Hernia.—The term "diaphragmatic hernia" indicates the escape of any abdominal organ through the diaphragm into the chest cavity. The condition may be either congenital or acquired. In the former case, it is due to an arrest of fetal development; in the latter, usually to traumatic rupture of the diaphragm by a blow or a stab wound, although in some instances it may result from excessive intra-abdominal pressure, as in vomiting. Many cases of the congenital variety have been described since the use of *x*-rays in diagnosis. In such cases, after a barium meal, the observer is surprised to find the stomach and intestines within the thorax. Hart gives the following list of the organs and tissues which may be thus displaced, in the order of frequency of the reported cases: stomach, omentum, colon, small intestine, liver, duodenum, pancreas, cecum, and kidney.

Symptoms.—The prominent symptoms of *congenital diaphragmatic hernia* are dyspnea and cyanosis. The heart is often displaced and a gurgling of gas can be heard in the chest. The usual tympany in the left hypochondrium may be absent. The majority of infants in this condition die when only a few days old, often before a diagnosis is made. Even if the diagnosis is made, however, no treatment is of sufficient avail to be noted, although the maintenance of an erect position and rectal injections have been advocated.

The initial symptoms of *traumatic hernia* of the diaphragm are those of shock, severe pain in the lower part of the chest, and a feeling of constriction. Hiccup and, often, dyspnea and vomiting are present. If the condition is due to a stab wound, pleurisy or peritonitis may result. The movements of the affected side are limited, the heart is displaced, a tympanitic note due to the presence of the stomach or intestines in the pleural cavity may be heard over the base of the lung, and often gurgling sounds due to the movement of flatus may be heard within the chest. *x*-Ray examination after a barium meal gives conclusive evidence of the presence of the abdominal viscera in the pleural cavity.

Prognosis.—If the hernia is the result of a stab wound the outlook is extremely serious. In other cases, however, the condition may exist for years without serious disadvantage. Strangulation is always to be dreaded, and serious compression or displacement of the lungs and heart from distention of the incarcerated organs with gas or from the entrance of more organs through the hernial opening may lead to a fatal termination.

Treatment.—The treatment of acquired diaphragmatic hernia is surgical.

Eventration of the Diaphragm.—The term "eventration of the diaphragm" indicates a defect which is characterized by a thinning or relaxation of one leaf of the diaphragm which occupies an abnormally high position. It is associated in some instances with aplasia of the lung on the affected side. The weight of evidence is that it is congenital in origin. This condition was first described by Petit in 1790. It is of rare occurrence, but during recent years a number of cases have been described.

Symptoms.—The symptoms of eventration of the diaphragm are indefinite. Some patients complain of a rather vague gastric distress. The condition is usually detected by *x*-ray examination. Funk has called attention to an increased outward movement of the costal margin on the affected side in inspiration, which is due to the fact that the intercostal muscles on

that side have little opposition from the weakened diaphragm. This observation has been confirmed by Korns.

TREATMENT.—Surgical treatment may be of value in certain cases.

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DISEASES OF THE KIDNEYS

ANOMALIES OF URINARY SECRETION

Anuria is total suppression of urine by the kidneys. The condition is generally the result of either (*a*) the extreme congestion associated with acute nephritis; (*b*) the mechanical obstruction of the genito-urinary tract by stone in the ureters or renal pelvices which may cause anuria on one side if the stone is unilateral, or complete anuria if bilateral, or by growths, usually cancerous, in the ureters; or (*c*) the marked degenerative nephritis caused by such chemical poisons as lead, mercury, and phosphorus. Rarely, merely the passing of a catheter has been known to bring on anuria by reflex nervous action.

In anuria the hydronephrosis which so frequently accompanies partial obstruction of the urinary tract does not tend to develop and there may be remarkably few *symptoms*. Headache, vomiting, and lumbar pain are the most common. Although non-protein nitrogen, urea, uric acid, and creatinin are retained in the blood, frequently in even larger amounts than during the terminal stages of uremia, convulsions occur rarely and consciousness is retained almost until death. The reason for this absence of convulsions and constitutional symptoms so characteristic of uremia is not known, but it must be remembered that the mere retention in the blood of any of the recognized non-protein nitrogen bodies is not in itself sufficient cause for uremia.

Anuria must be clearly differentiated from the condition in which urine is secreted by the kidneys and retained within the bladder. This distinction can be made by either physical examination or by catheterization. A tumor of the bladder palpable in the lower abdomen or stricture of the urethra may cause such retention of urine in the bladder.

The severity of anuria varies directly with the duration, which may be several hours or many days. Adams has reported recovery after total suppression of urine for nineteen days.

Treatment.—In the treatment of anuria associated with acute nephritis, hot applications, free purgation, and high hot colonic irrigations have proved valuable. Intravenous administrations of glucose (300 c.c. of a 20 per cent. solution twice a day) are also beneficial. Similar therapeutic measures are advisable when anuria is due to the extreme degeneration caused by chemical poisons. In the cases caused by stone or new growths surgical treatment is imperative.

Hematuria is the discharge of blood in the urine. In a small percentage of cases the source of the hemorrhage cannot be located, but in the majority, various available signs permit determination of the correct etiology.

Essential hematuria is the term applied to hematuria of unknown origin. In this, bleeding is usually spontaneous, painless, intermittent, and not so severe as to lead to exsanguination. Certain cases included in this group have been caused by varicosity of the veins of the kidney, pelvis, or papillæ. Urethral catheterization has demonstrated that the hemorrhage of essential hematuria is usually unilateral. *x*-Ray examination is always

negative. This condition is usually found in individuals of less than thirty years of age.

Hematuria of Known Etiology.—In by far the larger number of cases hemorrhage can be located and ascribed to a definite cause.

(*a*) *Renal Disturbances.*—Acute nephritis, pyelonephritis, and the acute exacerbations of chronic nephritis, especially when the kidneys are secondarily contracted, may be accompanied by hematuria of all degrees of severity. Passive congestion of the kidneys during marked cardiac failure is a common cause of the presence of a few red blood-cells in the urine. New growths, especially hypernephromata, cause profuse bleeding. In both early and advanced tuberculosis red cells as well as pus corpuscles appear in the urine, but without pyogenic organisms unless there has been secondary infection. Other causes of renal hematuria are: certain chemical agents, such as urotropin, turpentine, cantharides, and carbolic acid; the renal infarction secondary to endocarditis; and such systemic diseases as purpura, leukemia, and malaria.

(*b*) *Pathological Conditions of the Urinary Tract and Bladder.*—Among the most frequent causes of hematuria are stone in the ureter or bladder; tumors of the bladder or prostate; tuberculosis; ulceration; and rupture of the veins of the bladder. Occasionally gonorrhea may cause bleeding from the urethra.

(*c*) *Mechanical Disturbances.*—Traumatic rupture of the kidney, bladder, or posterior urethra, as well as injury of the urethral mucosa by catheterization, may also produce hematuria.

(*d*) *Other Causes.*—Strenuous exhausting physical exercise and exposure to cold are frequently followed by the temporary appearance of a few red blood-cells in the urine without other evidence of renal disorder.

Diagnosis.—In all types of hematuria red blood-cells, frequently crenated, and albumen are present in the urine. As blood-cells disintegrate rapidly in alkaline urine the reaction of specimens should be tested immediately after collection.

The exact character of the *urine* depends on the source of blood. There are several means by which this may be ascertained. If blood appears at the beginning of micturition it comes from the anterior urethra; if at the end, from the bladder as a rule; and if throughout micturition it is mixed with the urine, hemorrhage is from the kidney. In the latter case, blood-clots and blood-casts are present and the color of the urine varies from a smoky tinge to bright red.

Frequently, however, special examination is necessary before the point of bleeding can be exactly located. Lavage of the bladder through a catheter may provide evidence of renal hemorrhage by the persistent presence of blood in the washing fluid. Cystoscopy and urethral catheterization are also valuable in making the diagnosis.

Hemorrhoids as well as vaginal discharges may be confusing factors. A diagnosis of *essential hematuria* can be made only by a process of elimination, and should be accepted with reluctance.

Treatment.—Rest in bed, supplemented with full doses of morphin if necessary, is indicated in hematuria of whatever type. Cold applications to the lumbar region are often helpful. In certain cases of essential hematuria recovery has followed simple distention of the pelvis of the kidney with fluid, while in others intrapelvic lavage with silver nitrate and adrenalin

has proved of only temporary benefit. Nephrectomy should be performed only as an emergency measure in the most severe cases of unilateral bleeding.

Hemoglobinuria occurs when the blood-destroying organs are unable to hemolyze all the damaged red blood-cells in circulation and hemolysis consequently takes place in the blood-stream. Normally, the endothelial cells of the spleen, bone-marrow, and hemolymph glands take up these damaged corpuscles and deliver the hemoglobin which they contain to the circulation, whence it can be removed by the liver. Under these conditions the iron-forming fraction of the molecule is separated by hepatic action and retained for further use in the body, while the remaining portion is converted into bile-pigments and excreted. But as soon as the concentration of free hemoglobin in the blood-stream reaches a certain point (about 0.06 gm. of Hb per kilo of body weight—Pearce), the renal filter becomes ineffective and hemoglobin passes directly into the urine. Thus hemoglobin is a threshold substance, just as are the plasma chlorids. Factors which favor the passage of a large volume of fluid through the kidneys increase the excretion of hemoglobin, apparently by lowering the threshold level.

Hemoglobinuria falls into two groups: (*a*) Toxic and (*b*) paroxysmal.

Etiology.—The etiology of the toxic form is variable. Chemical poisons, such as carbolic acid, potassium chlorate, pyrogallic acid, carbon monoxid, muscarin, and cobra venom may produce rapid hemolysis; while the toxins generated by the exciting agents of certain infectious diseases not infrequently have a similar result. Those of scarlet fever, yellow fever, typhoid, syphilis, and certain types of hemolytic jaundice should be cited. In malaria, hemolysis is caused by the plasmodium which actually enters the red corpuscle, grows, and finally causes rupture. Sometimes hemolysis follows the introduction of foreign protein into the blood-stream, as, for instance, in transfusion and serum therapy or after extensive burns when the tissue proteins are partially split. Finally, exposure to cold and violent exercise are said so to increase the fragility of the red cells that hemoglobin is liberated and hemoglobinuria ensues.

When hemoglobin is present the color of urine varies from red to dark brown. If specimens are allowed to stand, a heavy brownish sediment precipitates. Microscopic examination of the sediment reveals no formed red cells, but the spectroscope demonstrates the characteristic bands of hemoglobin.

Treatment.—The form of treatment depends upon the etiology.

Albuminuria may be divided into various classes according to the etiology. In general, these fall under two headings—physiological and pathological.

Physiological Albuminuria.—*Orthostatic Albuminuria.*—For the type of albuminuria in which serum-albumen appears in the urine only after standing or sitting, and disappears after reclining, the term *orthostatic albuminuria* is employed. This type, which is most commonly seen in young patients, especially in girls, seems to occur usually in thin individuals with poor muscular tone and marked evidence of vasomotor instability.

There are two main theories as to the *etiology:* (1) That of Erlanger and Hooker, which ascribes the albuminuria to diminished pulse pressure; and (2) that of Jehle, which is based on the belief that the increased lordosis frequently present interferes with the renal circulation. Careful studies have shown that no disturbance of kidney function is involved.

The quantity of albumin in the urine varies from a heavy trace to as much as 8 to 10 gm. per liter. Casts are rarely present.

It is interesting to note that during orthostatic albuminuria, when the body is horizontal, a low pulse pressure artificially produced by mechanical lordosis causes albumen to appear in the urine.

In many patients the condition is outgrown or disappears as the general state of health improves; in others, correction of lordosis with a spinal brace is beneficial. The prognosis is good.

Pathological Albuminuria.—(1) *Secondary to Nutritional Changes.*—Normally the kidneys do not permit transmission of serum albumin through the glomerular epithelium into the tubules, but circulatory changes may so alter the permeability of the membrane that the protein can pass. As soon as renal circulation is re-established, however, excretion of albumen stops. Albuminuria of this type occurs during passive congestion of the kidney, severe anemia, and after strenuous muscular work and cold bathing. The quantity of albumen eliminated in the urine is usually small. If casts are present they are of the hyaline or granular type.

(2) *Secondary to Toxic Action.*—Slight albuminuria accompanies the pyrexia of all the acute infections. The cloudy swelling of glomeruli which is caused by the toxemia rapidly disappears during convalescence. In this type the urine may contain a few casts.

Chemical poisons also produce varying grades of albuminuria by their action upon the kidney. Mercury, lead, ether, and chloroform are the more common of these.

(3) *Associated with Definite Lesions of the Genito-urinary Tract.*—(*a*) In such organic diseases of the kidney as acute, subacute, or chronic nephritis the degree of albuminuria varies greatly. During advanced chronic interstitial nephritis with primarily contracted kidneys only the faintest trace of albumen may be excreted, while during nephritis of the chronic parenchymatous types, when the contraction is secondary, very large amounts are present in the urine. In suppurative nephritis, amyloid or fatty degeneration of the kidney, and as the result of many new growths in the kidney, albuminuria occurs as well.

(*b*) It also follows infection of the renal pelvis, ureter, bladder, prostate, and urethra.

Albumosuria.—When proteoses enter the blood-stream the tissues seem to be unable to use them and they appear in the urine. This is known as albumosuria or proteosuria. It is a condition associated with the rapid breaking down of tissue, such as occurs in suppuration of all kinds, intestinal obstruction, severe burns, resolution of pneumonia, involution of the uterus, acute yellow atrophy, and leukemia. In chronic degenerative parenchymatous forms of nephritis, globulin is excreted in considerable quantities.

Myelopathic albumosuria is the presence in the urine of a protein first described in 1848 by Bence-Jones as a "new substance." This is not a true albumose, but is allied to the more simple proteins. It seems to be definitely related to diseases of the bone, and appears in the urine of about 80 per cent. of the cases of myeloma. During leukemia, chloroma, myxedema (one case reported by Fitz), and nephritis it has also been found present in the urine.

The quantity recovered in the urine bears no relation to diet. The

output is constant throughout the twenty-four hours, and in some cases of myeloma amounts to 30 to 70 gm. daily. Just how the kidney can excrete such quantities without organic change or simultaneous liberation of serum albumen is difficult to explain.

The exact source of this Bence-Jones protein is not known, but the fact that the body cells react to its presence by the formation of a "precipitin" proves it to be synthetic. It coagulates at temperatures between 49° and 60° C.; does not dialyze; is precipitated from urine containing 25 per cent. nitric acid in such a form that it disappears on boiling, but reappears on cooling; and gives up sulphur in the presence of alkalies.

Prognosis.—Within recent years our interpretation of a small quantity of albumen in the urine has undergone a change. In young patients albuminuria cannot be considered pathological until the possibility of cyclic or orthostatic albuminuria has been excluded. A trace of albumen in the urine after the fortieth year may be merely an evidence of the retrogressive changes of age and frequently goes hand-in-hand with the slight rise in blood-pressure which is physiological. If associated with increased arterial tension, or the presence of casts or red blood-cells in the urine, albuminuria is of significance, but cannot be truly evaluated without careful consideration of the past history and physical condition of the patient.

Treatment depends upon the etiological basis of the condition. Multiple myelomata run a fatal course. Benzol has been advocated as a therapeutic measure for this type of albumosuria in leukemia.

Bacteriuria.—It is well known that a few bacteria frequently filter through the kidney epithelium and are passed in the urine without causing any symptoms or cellular reaction. When large numbers appear in the urine the condition is termed "bacteriuria" or "bacilluria." This is of two types—primary and secondary. The primary, which is the more common, is associated with cellular reaction, and is caused by a focus of infection in the genito-urinary tract. The urine is characteristically cloudy when voided and contains pus cells. When the cause of the condition is tuberculous pyogenic organisms are usually absent. Secondary bacilluria is not uncommon in the acute infections in which there is a general systemic distribution of the organisms. It accompanies typhoid fever, pneumonia in many cases, and the early stages of meningococcic meningitis.

Treatment.—Although treatment of primary bacteriuria is unsatisfactory, urotropin and autogenous vaccines are of value. In the secondary type the only specific medicine necessary is urotropin.

Pyuria is the presence of pus in the urine. It is a condition associated with infection of any part of the genito-urinary tract, from Bowman's capsule in the kidney to the external meatus of the urethra.

The *causes* fall naturally into three groups: (*a*) pyelitis, pyelonephritis, and pyonephrosis; (*b*) cystitis; (*c*) urethritis of gonorrheal or other origin, and tuberculosis or rupture of abscesses of the genito-urinary tract.

The presence of significant quantities of pus in the urine is evidenced quite definitely by cloudiness at the time of voiding; by the precipitation on standing of a stringy, grayish precipitate which can be differentiated from the phosphates with heat and acid, and from the urates by heat alone; and by the presence of albumen. Microscopic examination is, of course, the surest test. Normal urine contains only a few well-preserved leukocytes.

In determining the exact cause of pyuria several facts must be kept in

mind. During pyelitis and the pelvic inflammation produced by a calculus, pyuria is usually constant. That resulting from tuberculosis of the genito-urinary tract is also persistent. During pyonephrosis and the conditions associated with large abscesses of the kidney, on the other hand, pus may be discharged intermittently into the urine. The chemical reaction of urine in the pyuria caused by cystitis and tuberculosis of the genito-urinary tract is acid. Pyuria of tubercular origin is not accompanied by bacteriuria. Large quantities of pus may be present after rupture of an abscess into the genito-urinary tract. Certain confusing factors must always be considered before diagnosis is made definite. Differentiation between cystitis and chronic prostatitis or abscess of the prostate is necessary. In the female the absence of leukorrhea should be ascertained by inspection and catheterization.

Treatment.—Although specific treatment depends upon the etiology of the condition, an abundant fluid intake and autogenous vaccines are very beneficial in many cases of persistent pyelitis and cystitis.

Chyluria, Non-parasitic.—Chyluria and lipuria of non-parasitic origin are essentially the same. In both there is fat in the urine. The only point of difference is that in chyluria none of the fat is visible as minute droplets, while in lipuria some is so separated.

Fat is present in the urine more commonly than was formerly supposed. Although small amounts are frequently found in the urine of patients with *diabetes mellitus* when it is accompanied by lipemia and nephritis, especially of the parenchymatous type, as much as 6 per cent. has been reported present in some cases. It is thought that this fat passes directly from the blood through the kidney epithelium into the urine. In certain types of nephritis extensive fatty degeneration of the kidney cells results in the appearance of a large quantity of non-visible fat in the urine.

Mechanical blocking of the lymphatic system is, as a rule, the cause of the more marked cases of chyluria in which the urine is opaque and whitish like milk. Generally by rupturing the deeper lymphatics of the kidney it produces a "leak" in the kidneys or bladder through which fat enters the urine. Osler has reported a case in which obstruction of the thoracic duct was followed by rupture of the lymphatic vessels leading to the bladder. Such chyluria is more marked after meals, increases on reclining, and is frequently associated with hematuria. The simultaneous elimination of blood and fat in the urine is known as *hematochyluria*.

In the *diagnosis* of non-parasitic chyluria great care must be used to exclude *Filaria bancrofti* from the number of etiological agents.

Creatinuria, or the presence of creatin in the urine, has not as yet been fully explained. During early childhood it is normal for both sexes. In the normal male creatinuria ceases permanently at about seven years of age; in the female, on the other hand, it persists until puberty, and recurs with each menstrual period, during pregnancy, and during *postpartem* involution of the uterus.

Although many of the phenomena involved in the transformation of creatin into creatinin are known, the exact metabolism and source of these substances is an unsolved problem. Creatin is present in the body in large quantities: the voluntary muscles contain the highest concentration, the brain and testes are next in order, and in the circulating blood the concentration is lowest. Muscular exercise seems to have no effect upon the rate of excretion of creatin, but variations in the ability of the muscles to utilize

carbohydrate have a marked influence. Creatin appears in the urine, for instance, during the muscular dystrophies and atrophies accompanied by diminished carbohydrate metabolism. In such conditions as fasting, or *diabetes mellitus* when the carbohydrate and glycogen depots are exhausted, creatinuria also occurs, as well as in cancer of the liver, cyclic vomiting, fever, certain pituitary disturbances, and phosphorus and hydrazine poisoning. Hypoglycemia and creatinuria seem to be closely related. Although the significance of creatinuria is not known, careful studies have demonstrated that it is not an index of cellular destruction.

Lithuria.—The presence of excessive amounts of uric acid or urates in the urine is called lithuria.

In man and the higher apes uric acid is the end-product of the breakdown of the nucleic acid which is contained in certain protein molecules. Uric acid circulates in the blood-stream as a monosodium salt, for the most part in colloidal or protein combination (Benedict). It is excreted easily by the kidney in the form of sodium, potassium, and ammonium salts. These urates form a pinkish precipitate upon standing, which is soluble in urine when heated and appears under the microscope as amorphous granules. Frequently, however, acid phosphates are present in the urine in such high concentration that the basic radical is withdrawn from these salts, and uric acid precipitates in the characteristic crystals known as "cayenne pepper grains." These may be colorless, but are usually a rich mahogany brown because of the pigments in the urine. The factors which favor precipitation of uric acid are: (1) acidity, (2) concentration, (3) the presence of large amounts of neutral phosphate, and (4) increased excretion of uric acid. Both increased ingestion of foods rich in nuclein and increased catabolism of the nucleoproteins of the tissues augment excretion of uric acid.

The output of uric acid decreases immediately before an attack of gout, and increases greatly on the second or third day after onset.

Uric acid crystals and urates frequently take part in the formation of calculi.

Because of the better understanding of the solubility of uric acid, lithuria is considered of much less importance than formerly.

Treatment.—Administration of a diet free from purin bodies, which are found in meat, fish, liver, sweetbreads, brain, etc., removes the source of exogenous uric acid. Excretion of uric acid is increased by the salicylates, especially by atophan. Ingestion of alkalies reduces the acidity of the urine, and an abundant fluid intake lowers its concentration.

Oxaluria is the presence of undue quantities of oxalic acid and oxalates in the urine.

In 1838 Donné first described the calcium oxalate crystals contained in most acid urine. Subsequently, investigation has shown that the normal urinary output of oxalic acid (in the form of calcium salt) is between 15 and 20 mgm. per day. A majority of this is derived from food, but that part of it is the normal product of metabolism has been proved by the fact that during prolonged fasting the excretion of oxalic acid continues. Since the solubility of calcium oxalate in urine is independent of the degree of acidity and depends on colloidal conditions, and since urine is normally supersaturated with calcium oxalate, crystals of this salt may be seen in acid, neutral, and alkalin specimens.

Absorption of the insoluble calcium salt which is present in most vege-

tables is facilitated by the hydrochloric acid of gastric juice, and by excessive fermentation of carbohydrates in the intestine. Calcium inhibits absorption of the salt.

In certain individuals with so-called "oxalic acid diathesis" calcium oxalate stones tend to form. They usually develop first in the pelvis of the kidney, and are so hard and rough as to cause bleeding frequently.

Treatment.—The purpose of treatment is to facilitate solution of oxalates in the urine by increasing its acidity with double acid phosphates, raising the magnesium content, and lowering the calcium content. Consequently, the diet should contain little carbohydrate and oxalic acid. Rhubarb, spinach, potatoes, strawberries, beets, tomatoes, tea, coffee, and cocoa must, therefore, be avoided. Acid sodium phosphate increases the acidity of the urine most satisfactorily, and orally ingested magnesium salts raise the percentage of urinary magnesia.

Cystinuria.—A rare disturbance of the intermediary metabolism of protein results in cystinuria—the passage of cystin in the urine—or in the formation anywhere in the genito-urinary tract of calculi composed of cystin crystals. Under normal conditions cystin, which is an amino-acid containing sulphur, is broken down into simpler compounds, but during some metabolic conditions it is directly excreted.

The *occurrence* of cystinuria in members of three generations of one family is evidence of the possibility that it is caused by some hereditary condition.

Cystin was first discovered by Wollaston in 1910 in a urinary calculus. The typical hexagonal crystals which form in the urine are soluble in concentrated mineral acids and alkalies. Cystin stones are often multiple and cast a clear shadow with *x*-rays. Unless these stones have formed, cystinuria is accompanied by no symptoms. The tyrosin and leucin crystals which appear in the urine of some patients are evidence of a still more far-reaching abnormality of metabolism.

Treatment.—During cystinuria the fluid intake should be abundant, and the protein content of the diet low. Administration of alkali (6–10 gm. of sodium bicarbonate per day) is advisable. Such treatment is followed by disappearance of cystin crystals from the urine.

Phosphaturia.—Normally, the kidneys excrete between 1 and 5 gm. of phosphoric acid (P_2O_5) in the form of phosphates, but at times either this elimination becomes excessive or the phosphates are precipitated by a change in the reaction of the urine. Such abnormal excretion and precipitation is called phosphaturia. The phosphates thus excreted are of two types, the alkaline (Na, K) and the earthy (Ca, Mg). The most abundant are the sodium compounds which play an important part in the regulation of the acid-base equilibrium of the body. Calcium phosphate is the most important of the earthy salts.

Undue precipitation of phosphates occurs when infection of the genito-urinary tract is accompanied by the excretion of alkaline urine. It frequently results in the formation of stones in the bladder, renal pelvis, and urethra. These are usually composed of crystals of ammonium magnesium phosphate, calcium phosphate, calcium oxalate, and ammonium urate. The magnesium salt is the most abundant.

During phosphaturia the urine is alkaline and cloudy when voided, but clears on the addition of acid. The earthy (Ca, Mg) phosphates present are

converted by heat into monocalcium and tricalcium phosphates. These produce a fine turbidity which disappears when acid is added.

Treatment should remove any infection present, and lower the intake of calcium, which renders the phosphates more soluble. Acid sodium phosphate or urotropin should be administered in order to make the urine acid. A free fluid intake is advisable.

Indicanuria.—The term "indicanuria" is applied to the appearance of indican in the urine in comparatively large quantities only, for as much as 12 mgm. per day is excreted by the normal individual.

Urinary indican is derived from the indole generated by bacterial putrefaction in the body. The action of the colon bacillus upon tryptophane, an amino-acid which is present in the intestine, is of especial importance in this process. The indole is absorbed by the blood, oxidized, and joined with potassium sulphate in the liver to form indoxyl and, finally, indican.

Indicanuria is the best index of intestinal putrefaction and is most marked during obstruction of the small intestine. It occurs whenever pus collects in the body, as well as during peritonitis and some wasting diseases. Excretion of small amounts of indican is normal in the newborn.

Because of the slight toxicity of indole and indican, constitutional *symptoms* do not develop until considerable quantities have been absorbed.

Indicanuria is demonstrated by a simple test which consists of the addition of a strong oxidizing agent and subsequent shaking with chloroform. The indigo which forms from indican (potassium indoxyl sulphate) in the presence of the oxidizing agent gives its characteristic blue color to the solution containing chloroform.

Melanuria.—In certain pathological conditions the production of excess melanin, the normal coloring-matter of the skin, hair, and choroid of the eye, results in the appearance of this pigment in the blood and urine, *i. e.*, in melanemia and melanuria. This occurs during the course of Addison's disease and also in rare cases in which local degeneration of the tissues of melanotic tumors liberates large quantities of melanin. In the latter case as much as 500 gm. may be present in the body. Melanin is normally very abundant in the skin of the black races, and it has been estimated that the skin of a single individual may contain 1 gm.

Probably the *source* of the several closely related bodies now classified as melanin is certain chromogen groups of the protein molecule and not hemoglobin.

Although urine which contains melanin may be darkly colored when voided, its appearance is usually normal. This is explained by the fact that the melanin circulating in the blood is reduced by the liver to colorless melanogen—a substance which turns black when exposed to air or to other oxidizing agents. Urine may be colored dark brown by only 0.1 per cent. of melanin.

According to Helman, the presence of true melanogen in the urine can be determined by three reactions: the precipitation of a black substance on the addition of ferric chlorid; the solution of this substance in the presence of sodium carbonate to form a black solution; and the formation of a black or brownish powder when mineral acid is added to the black carbonate solution. All of these tests must be positive before melanogen can be said to be present.

Alkaptonuria, or the presence of alkapton in the urine, is rare, generally

persists throughout life, and is more common in the male than in the female. It is the result of a harmless anomaly of the intermediary protein metabolism which appears to bear some relation to the recessive characters of Mendelian inheritance. First-cousin marriages have frequently produced alkaptonuric offspring.

Although the *clinical manifestations* of alkaptonuria were well described by Marcet in 1823, the presence of alkapton or homogentisic acid in the urine was not recognized until 1887. At this time Marshall isolated the substance in the urine, but called it glycosuric acid. Its principal precursors are the tyrosin and phenylalanin of the protein molecule. Relatively as much is produced by endogenous protein as by that contained in the food, although, of course, the actual quantities derived from the two sources are of very different magnitude. Normally, alkapton is broken down by the tissues of the body—probably by the liver alone—before excretion, but in certain individuals it may be isolated in the circulating blood and is eliminated in the urine as an ammonium salt.

Urine which contains alkapton stains the linen, tends to turn dark when exposed to the air, and is frequently dark when voided. If mixed with an alkali it becomes black. The addition of dilute ferric chlorid solution drop by drop produces a transitory blue coloration. Such urine reduces Fehling's solution atypically, does not ferment, and is optically inactive.

In rare cases of alkaptonuria the cartilages turn dark. Since nonspecific fixation of the blood is often associated with the excretion of homogentisic acid, great care must be used in interpreting the Wassermann reaction when patients are known to be alkaptonuric.

Treatment.—As a rule there are no subjective symptoms which require treatment. Fluids should be taken freely, and, if desirable, the quantity of alkapton in the urine may be reduced by decreasing the protein content of the diet.

Pneumaturia is the passage of gas with the urine. It is known to occur after irrigation of the bladder and following cystoscopic examination of patients in the knee-elbow position, as well as during chronic cystitis. When the gas is derived from an extraneous source, its appearance in the urine is only temporary, for elimination is hastened by rapid absorption into the blood. Intravesical generation of gas is most common during chronic cystitis and is caused by gas-forming organisms—the colon bacillus, the yeast fungus, or the *Bacillus aërogenes capsulatus*. In such cases the urine is foamy when voided, and usually contains sugar. Rarely vesicointestinal fistulæ are associated with a cystitis of this type.

The *symptoms* are usually those of mild cystitis. The urine may be foamy when voided, or the gas may be passed at the end of micturition.

Pneumaturia may be demonstrated by the passage of urine under water or by submerging the end of the catheter.

Edward H. Mason.

PAROXYSMAL HEMOGLOBINURIA

Definition.—Paroxysmal hemoglobinuria is a rare disease characterized by transitory hemoglobinuria following exposure to cold or occasionally

after exertion, and by the presence in the blood of an autohemolysin which unites with the red blood-cells only at a low temperature. The disease is a manifestation of late syphilis, either congenital or acquired.

History.—In 1854 Dressler wrote about "intermittent albuminuria and chromaturia," and set forth the first good description of paroxysmal hemoglobinuria. During the last half of the nineteenth century numerous reports appeared. The clinical features were well defined, and the disease soon became generally recognized as an entity. Donath and Landsteiner (1904) made an important contribution when they observed that the blood of these patients contains an autohemolysin which may be demonstrated by a simple *in vitro* test.

Etiology.—Syphilis is now accepted as the essential cause of the disease. The paroxysmal hemoglobinuric may or may not show other signs of late syphilis, but the Wassermann reaction is almost invariably positive. Nearly all of the reported cases have occurred either in children with congenital lues or adults long past the secondary stage of acquired syphilis. The characteristic autohemolysin may be found in certain other syphilitics, especially in patients with general paresis who have not had hemoglobinuria. Despite the association of a positive Wassermann reaction with the presence of an autohemolysin, the two reactions have been shown to depend on different constituents of the serum.

Pathology.—Although paroxysmal hemoglobinuria is intimately related to late syphilis, it is possible by appropriate methods to remove from the blood the *autohemolysin* without weakening the Wassermann reaction. The titer of the autohemolysin in the serum may show variation from day to day; it may persist after the patient has ceased to have paroxysms upon exposure to cold. In the serum from different patients it shows varying degrees of thermolability. The writer has studied one patient whose autohemolysin was destroyed at 47.5° C. for thirty minutes so that fresh complement failed to reactivate it. A specimen from another patient was not destroyed at 55° C. for thirty minutes. The blood of the paroxysmal hemoglobinuric contains an isohemolysin, probably identical with the autohemolysin; at least, efforts at separation have been unsuccessful.

The *Donath and Landsteiner phenomenon* reveals one of the fundamental features of the mechanism which operates during a paroxysm. The test-tube reaction in its simplest form is carried out by chilling the patient's blood to about 5° C. for ten minutes and then warming it to 37° C., when hemolysis occurs. Normal blood so treated shows no hemolysis. Since the reaction requires complement which in human blood is usually not abundant, more constant results are obtained if one separates the serum, makes a suspension (5 or 10 per cent.) of the red blood-cells, and adds fresh guinea-pig complement. In the test-tube reaction more hemolysis occurs if a heavy suspension of red blood-cells is used and if the chilling is of short duration—seven to ten minutes rather than thirty to sixty minutes. Slight union of the autohemolysin with the corpuscles may occur at a temperature as high as 16° C. With lower temperatures the union is more complete.

In the spontaneous paroxysm it seems quite probable that blood in superficial capillaries might be chilled to 14° or 16° C. Union of the autohemolysin and red blood-cells would then occur. In the presence of complement, which is increased with chilling, hemolysis results after the chilled blood has passed from the surface of the body to the higher temperature

of internal blood-vessels. Hemoglobinuria follows. The urinary findings occur whenever the free hemoglobin in the blood rises above the renal threshold of hemoglobin excretion. In case the hemolysis is so slight that the renal threshold is not exceeded an abortive paroxysm occurs—hemoglobinemia with mild symptoms and no hemoglobinuria, the so-called *petit mal* of hemoglobinuria. It requires hemolysis of about one-sixtieth of the total hemoglobin of the body to produce a hemoglobinemia which oversteps the renal threshold (Ponfick and Stadelmann). The appearance of urobilin in the blood results from the increase of free hemoglobin, the precursor of bile-pigments which, in turn, constitute the mother substances of urobilin. Extrahepatic formation of bile pigment or excessive production in the liver explains the slight jaundice not infrequently seen following the paroxysm.

Symptoms.—Between the chilling, which may be surprisingly slight, and the onset of the paroxysm there is a *latent period* varying from a few minutes to six or eight hours. During this time the leukocyte count may drop to 2000 or 3000, with a relative increase in lymphocytes. With the onset of the attack the number of lymphocytes decreases and a slight polymorphonuclear leukocytosis occurs. The attack consists of malaise, often headache, pain in back and legs or abdomen, chilly sensations or a shaking chill, transitory fever during which the temperature may be 104° F. or higher, and cyanosis. Some patients show a temporary rise in systolic and diastolic blood-pressures of 50 to 100 millimeters of mercury. Frequently the liver and spleen enlarge during an attack. In a few cases the phenomena of Raynaud's disease are associated with the attacks. The urine is dark red or Burgundy color, often described as black by the patient. It contains hemoglobin, methemoglobin, and hyaline, granular and pigment casts, and urobilin. In freshly passed specimens intact erythrocytes may be found. The hemoglobin may be present in only one specimen of urine or it may appear for a day or two. Following the attack *mild jaundice* is common. In the interval between attacks the patient may be in good health, but not infrequently there are symptoms due to other manifestations of late syphilis. When attacks have been repeated at short intervals *secondary anemia* is commonly present.

Diagnosis.—The history of transitory excretion of dark-colored urine during the winter months, following exposure to cold or exertion; a positive Wassermann reaction and stigmata of late syphilis; the Donath and Landsteiner reaction in the drawn blood; and the artificial production of an attack by immersion of hands or feet in ice water provide the data which establish diagnosis. Without a positive Wassermann reaction the diagnosis is uncertain because there are other types of transitory hemoglobinuria unassociated with syphilis; for instance, the *Marsch-hämoglobinurie* (Fleischer, Schellong), in which the paroxysm is induced by a long march or walk. The writer has observed one case of this type in a college student. A brisk walk of several miles sufficed to bring on a paroxysm of hemoglobinuria with hemoglobinemia, similar to the attacks of the syphilitic hemoglobinuric. His health was otherwise excellent; other forms of exercise were without effect; there was no evidence of syphilis; the blood did not give the Donath and Landsteiner reaction. The hemoglobinuria of chronic malaria is also to be differentiated.

Treatment.—Various forms of therapy have been advocated: autoserotherapy (Widal, Abrami, and Brissaud); graded cold foot baths (Salen);

and administration of calcium chlorid or calcium lactate. These forms of treatment lack the rational basis and have not been demonstrated to com pare in effectiveness with *antisyphilitic treatment*. The writer has observed 2 patients who after thorough antisyphilitic treatment passed through two consecutive winters in New York without an attack. In each case, however, both the Wassermann and the Donath-Landsteiner reactions remained positive, though weakened. The patients were treated with many arsphenamin injections, mercury, iodids, and bismuth. This result corroborates the observations of Jones and Jones.

George M. Mackenzie.

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UREMIA

Definition.—Uremia is an intoxication induced by renal insufficiency. The majority of cases occur as a complication of nephritis, but uremia may be the sequel of urinary suppression from other causes; for example, renal calculi or prostatic disease. In France the term is used to denote an increased concentration of urea in the blood, but elsewhere the clinical syndrome is thus designated.

Etiology.—Provost and Dumas (1821) observed an accumulation of urea in the blood after bilateral nephrectomy in dogs. This observation led Bright's associates, Prout and Babbington, to test the blood of patients suffering from Bright's disease. They detected an increase of urea—hence the name uremia. Bright believed urea to be a very toxic substance and the cause of the severe nervous disorders noted in the later stages of some cases of albuminuria. More extended study, however, has shown that urea is not a very powerful poison. The problem of the causation of uremia became fairly stated when it was found that complete anuria in man and the removal of kidneys in animals caused death, but not the conspicuous symptom observed in Bright's uremic patients—convulsions. Along with a broadening of the conception of renal disease and a more exact knowledge of disordered function there has developed some extension of this idea of uremia.

Morbid Physiology.—As a result of disease, impairment of renal function may be evidenced by deficient excretion of (*a*) water, (*b*) chlorids, (*c*)

phosphates, (*d*) urea, and other nitrogen compounds. The type of functional defect determines primarily the character of uremic manifestations. These physiological deficiencies are in some measure referable to various kinds of nephritis. The disorders of function manifested by the large white kidney are chiefly an impairment in the excretion of water and salt, and consequent accumulation of water in the tissues, which is notable clinically as edema and anasarca. When this condition is prolonged, extreme edema of the brain produces first somnolence, and finally coma. A second type of nephritis is characterized by an insufficient nitrogen excretion which is shown by an increase of urea and non-protein nitrogen in the blood. When the insufficiency is severe a urinary poisoning results which produces symptoms somewhat analogous to those of prolonged anuria. That urea alone is somewhat toxic was demonstrated by Hewlett, who took enough to raise the blood-urea to 200 mgm. per 100 c.c. of blood. The symptoms which he experienced were nausea, headache, apathy, and somnolence. In this retention type of uremia there is often a retention of phosphates as well as of nitrogen. The phosphorus retention may be in some degree responsible for the acidosis which has been observed in some cases. The lack of adequate formation of ammonia would aggravate this tendency (Rabinowitz). It is of special interest in this relation that there was no acidosis in the cases of fatal mercuric nephritis with anuria studied by Loebel, which is in contrast with nephritic retention. The third type of uremia seems to be induced by a product of abnormal metabolism; retention of nitrogen may be present also, although not invariably. Clinically the specific manifestation is epileptiform convulsions. This type of uremia appears to be associated with glomerular nephritis. A toxic substance has been found in the blood of individuals with this type of disease (Foster).

Since the lesions in nephritis are often not confined to one renal element it happens that several types of insufficiency may occur together. The corresponding uremic symptoms are those of the various types.

Symptoms.—The symptoms of uremia fall into three main groups—toxic, psychic, and neuromotor. In some combination, depending on the nature of the basic renal disease, a single case represents a complex of these groups. The symptoms which seem directly referable to *general intoxication* are headache, lethargy, vomiting, and diarrhea. In some instances these may be the only manifestations, but in many they are associated with psychic or motor disorders. The *psychic disorders* range from mild delirium to pronounced hallucinatory-paranoid states, stupor, and coma. Of the *neuromotor manifestations* the most striking are the epileptiform convulsions. The attacks may occur without warning, or they may be preceded by twitching movements of the extremities. There may be transient paralysis of a limb or, exceptionally, hemiplegia.

Headache of extreme severity is the most common subjective symptom of uremia, but it does not occur invariably. It may precede all other symptoms for weeks; indeed, it may be the only indication to the patient that he is not in health. In association with constant nausea, occasional vomiting, restlessness, and nocturnal delirium it completes the clinical picture of the retention type of uremia. Even when headache is absent the restlessness is incessant, and although the patient is apathetic, even drowsy, at times, there is no sleep; the very sense of exhaustion seems to prevent sleep. At times the psychic state is remarkable. Nocturnal delirium is common.

Delusions and paranoid trends may prevail and necessitate restraint of the patient.

Besides nausea and vomiting there may be periods of *obstinate constipation* alternating with *intractable diarrhea*. Though no peculiar substance has been discovered in the discharges, it is an old clinical aphorism that uremic diarrhea should not be checked. Occasionally diarrhea or persistent vomiting is the first symptom and may be misleading in diagnosis.

Dyspnea of several varieties is a frequent symptom. In some cases this appears to be caused by acidosis; in other cases acidosis is not detectable. The *heart* is so frequently affected in chronic nephritis, especially in individuals past middle life, that myocardial insufficiency may be the cause of respiratory symptoms. The dyspnea of uremia may occur in attacks, usually at night, or may be moderate and continuous. If uremia is protracted, *Cheyne-Stokes respiration* may persist for weeks.

When the progress of *retention uremia* is unfavorable there is a gradual transition from *apathy* and *torpor* to *stupor* and *coma*. Coma may develop rapidly, especially when uremia is precipitated by some accident, infection, or surgical operation. The contrast between the uremia consequent to nephritis and that which results from anuria (of stone, mercury poisoning, or bilateral nephrectomy) is most striking. With the latter, death creeps on peacefully, often without attendant suffering. Headache is rare, nausea and vomiting do not occur except as a result of mercuric gastro-enteritis. Psychic disorders are absent. There is only increasing weakness and deeper sleep which closes the scene.

In that type of nephritis which is characterized by *retention of water and chlorids*—the large white kidney—*edema* is the conspicuous sign. There is no significant nitrogen retention; and when uremia occurs toxic symptoms are lacking. The patient becomes increasingly sluggish mentally, then stuporous, and finally comatose. Headache is seldom present, and if there be dyspnea it is usually due to fluid in the pleural or pericardial sacs.

Epileptiform uremia presents the most clearly defined clinical picture of the various types. Especially is this so when nephritis develops in a child as a sequel to an acute infection. The primary infection may have been mild. It is often spoken of as a cold. The temperature is raised for a day or two, then the patient is allowed to leave his bed. A week later some edema is noted, perhaps of the face only, or of the legs, and after a day or two there may be slight headache and hazy vision. Then suddenly there is a convulsive seizure. This is generalized, of the tonic clonic type, and resembles those of epilepsy or eclampsia accompanied by unconsciousness. Several convulsions may follow one another and terminate in death; or after a series of seizures the patient may gradually regain consciousness. Uremic amaurosis may persist for several days without detectable lesion of the retina or nerve head. There may be headache and vomiting, which subside quickly in favorable cases, and usually there is a slight fever. The convulsive type of uremia develops in the course of the acute nephritis following scarlet fever, tonsillitis, and pneumonia, or after an acute exacerbation of chronic nephritis.

Diagnosis.—When the patient has been under observation preceding the development of uremia there is seldom difficulty in recognizing the character of the disorder. But when the patient is first seen in coma or at

the time of a convulsive seizure, mistakes are frequently made. Since uremia is a sequel of nephritis, sufficient evidence of this condition must be available to justify the diagnosis of uremia. The character of the urine alone can seldom establish the diagnosis of nephritis. When cardiac insufficiency is absent, general anasarca, marked albuminuria, and the presence of casts in the urine might be adequate evidence of nephritis, but in uremia of the retention type there is likely to be some cardiac disorder sufficient to explain albuminuria at least. In disturbances of this type examination of the retina, the blood-pressure, and the blood chemistry seldom fail to give decisive data.

In part at least the diagnosis of uremia must be made by a process of exclusion. The principle in diagnosis is first to determine whether there is adequate causation (nephritis), then to exclude factors other than uremia which might produce the particular symptoms. *Cerebral hemorrhage* or *thrombosis of cerebral arteries* is apt to occur in the later stages of nephritis and give rise to symptoms suggestive of uremia. A terminal *streptococcus meningitis* is not rare. When there is a complicating nephritis, uremia may be confused with any disorder which induces *convulsions* or *coma*. *Cerebrospinal syphilis* is a common cause of mistakes, and *chronic alcoholism* induces a stuporous state which may persist for days and is often associated with nephritis.

The coma of uremia is sometimes mistaken for that of *diabetic acidosis*. Diabetes is apt to induce nephritis and many diabetic patients die of renal disease. The presence of sugar and ketones in the urine does not establish the cause of coma as diabetic, and unless other signs be present—especially softness of the eyeball—uremia rather than acidosis must be considered.

Convulsive seizures associated with albuminuria and slight edema are usually of uremic origin, but it is not uncommon to find albumin in the urine after severe epileptic attacks; and cerebrospinal lues usually develops at a period of life when renal disease is common. Cerebral arteriosclerosis is frequently associated with nephritis and gives rise to convulsions in some cases. If careful examinations be made—especially of the retina—and due consideration be given to all the facts, the correct diagnosis can usually be established. When there is no history available and the patient is seen first in coma or in convulsive seizures, it is necessary to wait before decision is made.

Treatment.—Failure to appreciate the physiological relations which occur in nephritis may allow uremia to develop. In nephritis with nitrogen retention either *restriction of the water intake* or the use of *hot packs* for diaphoresis is often hazardous. The result is to increase the concentration of waste products in the blood and tissues. Convulsive seizures may follow the *copious sweating* induced in the attempt to relieve the edema.

Since the renal function is dependent upon the circulation, and hence upon the heart, it is necessary—especially with older patients—to do all that is possible to aid cardiac efficiency. There are but few measures suited to this, and on that account it is advisable to use *digitalis* always during retention uremia. It is surprising how often there appears to be a cardiac element in uremia of this type.

In chronic nephritis, when uremia is an immediate result of prostatic retention, recovery often follows relief of the obstruction and a flushing of the system by copious water drinking. The use of a retention catheter

may be necessary until the patient is in condition for operation. The heart in these cases demands careful attention.

Chronic nephritis is subject to exacerbations attended by periods of decreased renal function sufficiently severe to cause uremic manifestations. Headache, which is often the warning symptom, is associated with nocturnal dyspnea. The patient should at once go to bed and in order to reduce protein metabolism the *diet* should be scant and composed chiefly of carbohydrate. If there be no nausea the patient should be urged to take as much water as possible—3 liters daily is not too much. For the headache, restlessness, and insomnia no drug equals *chloral*. At times vomiting is the chief symptom, and then it is better to withhold food and liquid by mouth for a day or more, and give glucose solution and water by rectum.

With a constantly increasing quantity of non-protein nitrogen in the blood it may be necessary to withdraw a pint or a pint and a half of blood and introduce a like amount of physiological saline solution. This measure has proved to be more useful in the convulsive type of uremia than in the purely retentive type. Recovery always depends upon the amount of functioning renal tissue.

Lumbar puncture, with the withdrawal of an ounce or two of fluid, is occasionally followed by striking improvement of the patient's condition. This procedure is necessary when there are signs of increased intracranial pressure, particularly in the retina and disks. The relief from headache in some cases may be prompt, and puncture is specifically required by the stupor and coma consequent to nephritis of the water-retention type.

Convulsions demand heroic treatment with little regard to the causative nephritis; *chloroform* and *morphin* during the seizures, with *chloral*, constitute the immediate methods of control. *Phlebotomy* has a theoretical basis, especially if fluid be introduced by vein and hypodermoclysis in order to dilute the toxins retained in the body. Since this type of uremia often follows the rapid subsidence of edema, it has always seemed advisable to introduce water into the tissues by every available method.

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NEPHRITIS

(Bright's Disease)

Definition.—Nephritis is a diffuse, progressive, degenerative or proliferative lesion involving in varying proportion the renal parenchyma, the interstitial tissue, and the renal vascular system. The word "progressive" is used to exclude slighter changes which occur in fevers and which rapidly clear up with subsidence of fever without progression into any lesion that impairs renal function.

The term *nephritis* implies inflammation; in a broad sense it means the reaction to injury, however caused, and includes degenerative changes as well as cellular infiltration and tissue proliferation. Various authors have criticised the term, but other names, such as nephropathy, nephrosis, etc., which have been suggested for the whole or a particular type of the disease, seem to be no better.

The ordinary types of suppurative processes are not included under the term *nephritis*.

Incidence.—Nephritis ranks high among causes of death, coming third or fourth in most statistics. It is a contributory factor in the death of many patients classified under other headings in tables of causes of death. Acute nephritis, though rarely fatal, is a fairly common disease. Chronic nephritis, besides being frequent, may be present and produce symptoms in the individual for long periods of time. The result is that individuals with some form of nephritis, which is a cause of part or the whole of the disability that brings them to their physician, constitute a considerable proportion of medical patients.

Etiology.—Infections and infectious diseases of various sorts are frequent causes of acute nephritis. Of these, *infections of the upper respiratory tract*, rhinitis, coryza, tonsillitis, pharyngitis, laryngitis, tracheitis, or bronchitis, most often precede the development of nephritis. Tonsillitis more commonly than any other disturbance is the cause of acute nephritis. *Scarlet fever* may be complicated or followed by acute nephritis. In all of the causes streptococci play an important rôle.

Exposure to cold sometimes seems a cause. This may be an indirect effect by way of an infection directly referable to the exposure.

Syphilis may cause acute nephritis, but this is rare. Some of these cases are more subacute than acute in type and show marked edema. A definite type of acute renal disturbance is caused by *pregnancy;* many consider that this is more correctly regarded as a toxemia of pregnancy than as a true nephritis. It has, however, many of the manifestations of nephritis. Certain *chemical substances*, such as uranium nitrate, corrosive sublimate, arsenic, lead, etc., cause a nephritis in animals. Of these, corrosive sublimate alone is of etiological significance to man. In many cases of acute nephritis no cause can be assigned.

When it comes to a consideration of chronic nephritis, knowledge is very much less definite. In some cases chronic nephritis has progressed from acute nephritis, but this is a surprisingly rare development, and usually chronic nephritis begins insidiously. The relation of *infections* to chronic nephritis is far from certain. It seems reasonable to suppose that infections play a large rôle, but proof of this is very unsatisfactory. Statistics, intended to show the frequency of antecedent infections as suggestive of a probable etiological rôle in chronic nephritis, generally omit any comparison of the incidence of the same infections in patients of similar age, free from nephritis. When such controls are considered, there is no evident difference between nephritic and non-nephritic individuals in relation to antecedent infections.

Syphilis apparently has very little causal relationship to chronic nephritis. The same holds for *tuberculosis*.

Recent *experimental studies* indicate that a high protein diet causes chronic nephritis. In man *overeating* probably plays a rôle, but there is no

very positive evidence for this. *Alcohol* seems to have nothing definite to do with it.

Vascular degenerative changes are intermingled in many patients with chronic nephritis and undoubtedly are often responsible for part of the renal lesion, but of the ultimate cause of the vascular lesions no more is known than of the cause of chronic nephritis.

Clinical Classification.—Many classifications of nephritis have been made. Most of them are too complex for accurate application in clinical work. This is especially true of those based on pathological lesions; it seems impossible, for the present at least, to infer, during life, with any great degree of accuracy, what the structural changes in the kidney may be, particularly if the finer details of structure are included. An etiological classification, however desirable it may be on theoretical grounds, is entirely unwarranted by present knowledge of the etiology of nephritis. The best classification that can be offered at the present time is a quite simple clinical grouping of patients so that those presenting certain fairly definite and easily recognizable peculiarities of symptoms and course will be grouped together. Such a classification is represented by the following, which has been found useful in the clinical management of patients:

Acute nephritis.

Subacute nephritis:

(*a*) Subacute nephritis with edema.

(*b*) Hemorrhagic nephritis.

Chronic nephritis:

(*a*) With edema.

(*b*) Without edema.

This grouping facilitates the description of nephritis and aids in a better understanding of the pathology, symptomatology, diagnosis, prognosis, and treatment of the disease. Acute nephritis and chronic nephritis without edema occur frequently; subacute nephritis is less common; chronic nephritis with edema is a rare disease.

ACUTE NEPHRITIS

Pathology.—During acute nephritis the kidney is somewhat larger than normal because of congestion, edema, hemorrhage, and swelling of the epithelial cells. The capsule strips easily, leaving a smooth moist surface; the cut surface is sometimes bloody; the color varies from pale translucent gray or yellowish gray to red; often the cut surface is mottled gray and red, depending on the amount and distribution of hemorrhage. When glomeruli are particularly involved, they may be seen as translucent gray or red points dotted over the surface of the cortex.

Histologically the glomeruli almost always show change. Hemorrhage from them is common. Many attribute the hematuria of acute nephritis entirely to glomerular lesions. Sometimes polynuclear leukocytes are found in the glomerular tufts in marked numbers; very often capillary endothelium or capsular epithelium proliferates, the former occasionally filling the vascular tufts with cells, and the latter producing so-called crescents that encroach on the space of Bowman. The capillary wall may show a hyaline transformation and gradually the lobulation of the tuft may increase with slight proliferation of connective tissue about the vessels, especially at their point of ingress and egress. Degenerative changes in the glomeruli are

probably very frequent, but usually cannot be directly demonstrated, though evidenced by the escape of albuminous material into the space about the vascular tufts. It is usual to find various types of glomerular lesions in the same kidney as well as different degrees of change in neighboring glomeruli.

The tubular epithelium may be swollen and abnormally granular in appearance, or it may show hyaline, colloid, or fatty degeneration. Necrosis of the epithelial cells may be found. Usually there is some evidence of regeneration shown by cells with more deeply staining cytoplasm and nuclei, but reparative processes, which are so prominent in the experimental nephritis of animals, do not seem to be very active in man. The lumen of the tubules may be greatly encroached upon or filled with exudate and cellular débris, the latter going to make up part of the structure of casts.

The interstitial tissue and blood-vessels show very little change in acute nephritis except edema, hemorrhage, and some cellular infiltration.

Symptoms and Physical Findings.—Acute nephritis may begin so insidiously that, except for changes in the urine, there is almost nothing to suggest its existence. On the other hand, however, there may be marked malaise, headache, nausea and vomiting, pain in the loins, fever, generalized edema, and a scant bloody urine. Most patients have slight malaise, loss of appetite, puffiness of the face, slight pitting edema, slight fever, and excrete a small amount of highly colored or smoky urine. Such patients frequently notice these symptoms, particularly puffiness about the eyes, for the first time on waking in the morning. These signs of acute nephritis often develop after some acute infection, particularly of the upper respiratory tract, and, as a rule, ten to twelve days subsequent to the onset of the infection. When the edema is marked the patients have a very typical, pale, pasty appearance, even though the blood shows very little real anemia. The edema of acute nephritis is soft and not distributed particularly in the dependent parts of the body as is that of cardiac disease, and only in extremely rare instances does it feel brawny. Not infrequently fluid collects, too, in the body cavities, especially in the abdomen, and sometimes there is considerable ascites with very little subcutaneous edema. The body weight may be considerably increased by the edema.

Some patients with headache have stupor, or are restless, sleep fitfully, and may show mild delirium. More rarely there is muscular twitching or even convulsive seizures followed by coma. A rare patient shows amblyopia without changes in the eye-grounds. Some become dyspneic and have Cheyne-Stokes' respiration. These are toxic manifestations, very generally grouped together as *uremia*. Some of these may result from cerebral edema and even be relieved by lumbar puncture.

The *blood-pressure* at times is normal, at times moderately increased; rarely it is high. A blood-pressure over 180 mm. of Hg, however, should arouse the suspicion of an underlying chronic nephritis in a stage of acute exacerbation as far as symptoms of acute nephritis are concerned. In acute nephritis such high blood-pressures, if they occur, do not persist. It is probable that no demonstrable cardiovascular change is present in acute nephritis; and if cardiac enlargement or arteriosclerosis are found, they probably antedate the acute nephritis.

In acute nephritis the *eye-grounds* may show slight edema of the nerve head or a few focal hemorrhages. Exudate is rare in the retina in acute nephritis. In most patients the eye-grounds are normal.

The *urine* in acute nephritis is usually decreased in amount, sometimes it is very scant; rarely there is anuria. It almost always contains some blood and is colored accordingly; this gives it a slight turbidity and a so-called smoky or dark brownish-red color; rarely it is bright red. Albumin is usually abundant, but the quantity may vary, so that on boiling or adding nitric acid, either a slight cloud precipitates or a bulky flocculent mass, which almost solidifies the urine, is formed. Fibrinuria is a rare finding. Casts are almost always present and abundant. They may disintegrate readily and so be overlooked, especially if the specimens examined are not just voided. They vary in type. Hyaline, granular, and cellular casts are found, usually mixed together. Coarsely granular, brownish casts are very commonly found. Red cells, leukocytes, and desquamated epithelial cells occur in varying number and ratio.

The output of *sodium chlorid* may be much decreased in acute nephritis, especially when edema is marked. When the urine is concentrated bladder irritation is not infrequent. Sometimes these symptoms are marked enough to suggest cystitis.

Phenolsulphonephthalein excretion may be normal or decreased. It is unusual to recover less than 30 per cent. in two hours. Occasionally the phthalein excretion decreases as the other evidences in the urine indicate improvement. *Blood nitrogen* determinations are at first normal; later there is an increase, so that 20 to 30 mgm. of urea nitrogen per 100 c.c. of blood is a common finding. Much greater increases are found, especially when the amount of urine is greatly decreased, but these are rather rare. The actual figure depends a good deal on the protein content of the diet, but in very severe acute nephritis blood nitrogen values may be raised by tissue catabolism even though the food intake is very low. The creatinin, uric acid, and amino-acid content is sometimes increased in the blood in acute nephritis, but the quantity of these substances present in the urine is of little practical value as contrasted with total non-protein nitrogen or urea nitrogen. In severe nephritis the total nitrogen of the urine may be increased by tissue catabolism. As the nitrogenous content of the diet is usually decreased during acute nephritis, the nitrogenous excretion usually falls.

Sometimes there is a fairly marked *secondary anemia*, but, as a rule, in acute nephritis the red cell count and hemoglobin estimations are almost normal. A slight leukocytosis may accompany the earlier acute stages.

Diagnosis from symptoms and urinary findings is usually easy. Orthostatic albuminuria must be differentiated, and this ordinarily can be done readily by absence of symptoms, lack of casts in the urine, and disappearance of the albumin when the patient remains in a prone position. When a few casts are found and the albuminuria has an orthostatic character, diagnosis becomes more difficult. It is safer to regard this condition as mild acute nephritis. During the active stage of *acute infectious diseases* albuminuria and cylindruria should be regarded as the result of degenerative changes in the kidney and not diagnosed as acute nephritis unless the edema is found to be of non-cardiac etiology and the amount of urine is markedly disproportionate to the fluid intake. It may be difficult to recognize an underlying chronic nephritis during the stage of activity of the acute process; final diagnosis should await the results of tests after convalescence is well established.

Prognosis.—The prognosis in acute nephritis is good. Few patients die; most children recover completely, though urinary changes may long persist. In adults some urinary changes often continue. Very occasionally the condition progresses into chronic nephritis, but there is no way to anticipate this development. In general, patients who have survived acute nephritis seem to have no real increased tendency to develop chronic nephritis subsequently.

Treatment.—There is no specific treatment. Prolonged rest in bed, in airy, cheerful surroundings, with a simple nutritious diet of relatively scant protein and salt content, but of normal caloric value, and a fluid intake of only 1200 to 1500 c.c. per day, constitutes all that can be offered in the way of treatment. In the more severe cases, especially those with nausea or anorexia, a diet limited to *milk* (amounts not exceeding 800 c.c. per twenty-four hours) is well suited to the first few days, but should not be continued for more than one week. Mild *catharsis* is desirable. *Diuretics* should be avoided. With anemia a little *iron* helps. Sweating, bleeding, and vigorous catharsis may be tried if there are signs of uremia. In most patients, however, it pays to withhold vigorous and particularly debilitating measures of therapeusis.

SUBACUTE NEPHRITIS

Subacute nephritis with edema is intermediate in manifestations and duration between acute nephritis and chronic nephritis. The changes in the kidney are likewise intermediary. For these reasons such cases are classified as subacute. Their chief feature is an early developing and a persisting generalized edema. As far as can be judged, subacute nephritis with edema corresponds clinically fairly closely to the nephrosis of other authors.

Pathology.—When death occurs early the kidneys are pale and swollen; when the disease has been of longer duration there is some shrinkage and the kidneys are smaller than normal, but never very small. Both types are usually smooth, and the capsule strips readily without tearing away tissue. Histological lesions in the glomeruli are extensive. They are usually both intracapillary and capsular in nature. Their exact appearance varies with the duration of the disease, for as time goes on the glomeruli become prominently lobulated, and still later manifest atrophic changes and capsular thickening. Degeneration of tubular epithelium is marked, and later the tubules atrophy. With these changes the interstitial tissue gradually shows proliferation and cellular infiltration. The main difference between the kidneys during this type of nephritis and during acute nephritis lies in the extent and dominance of glomerular lesions.

Symptoms and Physical Changes.—Early, progressing, subcutaneous edema, later with hydrops of the body cavities, especially ascites, is the striking feature of the disease. With edema is associated the characteristic, pale, pasty appearance without real anemia, at least in the early stages. Later there is a lowered hemoglobin and red cell count. The ascitic fluid often is opalescent and pseudochylous. Heart and blood-vessels show no changes in the earlier stages. Later, the blood-pressure may rise and evidences of arteriosclerosis appear. The edema, however, is renal, not circulatory in origin, until the late stages, when there is circulatory failure. The urine is decreased in amount, rich in albumin, and contains many casts of all sorts, including fatty casts. Red cells occur, but the urine usually

contains little or no macroscopic blood. Leukocytes are numerous. Though cellular elements usually are abundant, there is a type of case in which they do not appear freely in the urine and the casts are mainly fatty or hyaline, containing fat droplets. This type corresponds with the nephrosis of some authors. Sodium chlorid excretion is very low; blood chlorid is usually high. Small amounts of glucose often appear in the urine. Renal function, as measured by phenolsulphonephthalein excretion and blood urea nitrogen, is surprisingly good until the late stages of the disease. Sometimes early in the disease phthalein excretion may be above normal.

Toxic symptoms are very few. Late in the disease they may appear and are those of mild or marked uremia. Real uremia, however, is apt to be almost a terminal event. Weakness is the prominent symptom except for the discomfort incident to the edema. The main physiological change during the disease is an inability of the kidney to excrete water and salt.

Diagnosis is easy when the criteria just enumerated are kept in mind. The edema of *starvation* might simulate this process; or *serum sickness* and an occasional diffuse *angioneurotic edema* might be mistaken for it, but these ought to be easily enough recognized by the circumstances associated with them. Occasionally the symptoms of a water-logged cardiac with a slow regular pulse may closely simulate those of nephritis with edema; but cardiac enlargement suggests the circulatory origin of such edema and a therapeutic response to digitalis and diuretics will quickly clear up the diagnosis by producing a marked diuresis, which is in sharp contrast to the failure of diuretic response during renal edema.

Prognosis.—The prognosis is poor, for the disease progresses so steadily that many patients die in twelve to twenty-four months. Others largely recover from the edema, but later their condition progresses downward, as a chronic nephritis with failing circulation. A very few may recover.

Treatment.—The very rare cases of syphilitic etiology should be given antisyphilitic therapy. Except for these, treatment is essentially that of the edema. The patients need to remain in bed with abundant sunshine and fresh air. The *diet* should contain little fluid (1000 to 1200 c.c. per day) or sodium chlorid. It is necessary to maintain a full or even excess caloric value. Between 25 and 40 gm. of protein can be taken daily, and these quantities may later be increased if the blood urea nitrogen does not increase. When the disturbance is of the nephrotic type, administration of a diet rich in protein (120 to 240 gm.) and carbohydrate (150 to 300 gm.), and poor in fat (20 to 40 gm.), with blood transfusion, as advised by Epstein, gives satisfactory results. In other patients this diet may increase the blood nitrogen, and nausea may interdict the high protein intake. It is well to try such a régime with caution, not pushing it if the patient does not do well. It should be used chiefly when the phthalein excretion is not low and blood nitrogen not elevated. If the phthalein excretion is low and the blood nitrogen high, a diet low in protein (25 gm.) and rich in carbohydrate with a minimal amount of sodium chlorid is preferable. Sometimes every precaution to eliminate sodium chlorid from the diet must be taken if beneficial results are to be obtained.

To reduce *edema*, watery catharsis with magnesium sulphate or jalap is indicated when limitation of fluid and salt intake does not affect it, or when diuretics fail. To be effective it must be continued for days. In choosing a

cathartic, remember that some have a high percentage of sodium chlorid and so are not compatible with a diet primarily restricted as to salt content.

Sweating is theoretically indicated; practically, it helps only a little and its debilitating effect often counteracts any other benefit. If used, some form of electric light sweat bath is to be preferred. Sweating by drugs, such as pilocarpin, is undesirable. *Diuresis* is desirable, but can be rarely attained. As to diuretics, what has been said for the treatment of acute nephritis applies. Recently good diuretic effects have been reported from calcium, either the lactate or chlorid, in doses varying from 3 gm. up to 12 to 18 gm. per day, especially when followed by intramuscular injection of 1 to 2 c.c. of novasurol.

Fluid that by its presence causes discomfort or hinders respiration and circulation should be removed by mechanical means. This certainly applies to pleural and abdominal accumulations. A better urine output and a decrease in edema of the legs may result from the withdrawal of abdominal fluid which presses on the renal veins and the inferior vena cava and its branches. Drainage of subcutaneous fluid from the legs by means of Southey tubes or incisions down to the deep fascia may be practised when the edema is excessive and a cause of much discomfort. Infection is, however, difficult to avoid.

If there is reasonable doubt in regard to the presence of a cardiocirculatory factor in the edema, a therapeutic test with *digitalis* in full doses should be made. Digitalis so used does no harm even when the edema is entirely renal; it has no diuretic effect when there is no circulatory failure.

Hemorrhagic nephritis is characterized by persisting slight or moderate hematuria. It begins usually as an acute nephritis, but may persist for several years. It is grouped under subacute nephritis, even though in some cases it might properly be regarded as chronic.

Pathology.—In the few cases in which examination of the kidney has been possible there has been an increase of the connective tissue bands separating areas which are fairly normal as far as connective tissue is concerned. The glomeruli show lesions, increased lobulation, and thickening of the capsule, increasing to partial atrophy of the glomeruli with evidences of hemorrhage. Thromboses of glomerular capillaries are not infrequent. The tubular epithelium undergoes atrophy of varying degree, but little or no active degeneration.

Symptoms and Physical Findings.—The onset is usually like an ordinary acute nephritis, but instead of largely clearing up in a short time, the hematuria persists. There are no particular symptoms during the earlier stages except some weakness and malaise; later the symptoms of a progressing chronic nephritis may appear. Even with persisting hematuria anemia may long be absent and then develop very slowly. Although there is bleeding, there seem to be no toxic disturbances to hinder the reparative activity of the bone-marrow. The urine contains a slight amount of albumin, few or very many red cells, and an occasional hyaline, finely granular, or blood cast. The casts may be so few as to be difficult to find. Day in and day out the urine changes only in that it contains varying numbers of red blood-cells. This persisted in one of our cases for more than four years. Edema, as a rule, is present only in the beginning. The blood-pressure is generally normal except late in the chronic cases. Renal function is usually excellent except in the later stages of chronic disease.

Prognosis.—Numerous patients recover, though improvement may be slow. Most patients gradually fail as the chronic nephritis without edema continues.

Diagnosis is most important. It depends on the presence of a few casts, especially red cell casts, among the red cells, and requires patient, careful examination of the urinary sediment. Except for casts the urine is similar to that excreted in patients with papilloma of the bladder, painless renal calculus, hypernephroma, and tuberculosis unaccompanied by pus or cystitic symptoms. It is wise to exclude the possibility of these conditions by appropriate cystoscopic and *x*-ray examination if the evidences of nephritis are slight, since casts may appear in the urine because of slight accompanying renal changes. It is preferable to discommode a patient with probable hemorrhagic nephritis by the diagnostic methods of genito-urinary surgery rather than to overlook a bladder or renal condition that should be operated on.

Treatment is very unsatisfactory. The general hygienic and dietary measures employed for nephritis are applicable. There seems to be no reason for marked restriction of any of the constituents of the diet. Rest in bed, prolonged for months, is indicated. Nothing except this seems to have any definite effect on the bleeding. In our experience, ergot, calcium, transfusion of blood, vaccines, even renal decapsulation are all of no avail. Some authors report prompt cure from tonsillectomy, which is contrary to our experience.

CHRONIC NEPHRITIS

Chronic Nephritis with Edema.—No very sharp line can be drawn between subacute nephritis with edema and chronic nephritis with edema. The chronic form, as a rule, is more insidious in onset; the progressive development of edema is more gradual and the urinary sediment shows less evidence of activity as indicated by the presence of cellular elements and granular and cellular casts; its duration is longer, but in most cases does not exceed three or five years, unless there is a gradual change to the more persistent type of nephritis with high blood-pressure and slight or no edema.

Pathology.—The kidneys are usually somewhat shrunken and may be quite small. The surface, however, is not very granular. The color is pale rather than red. The capsule strips with some difficulty and leaves a roughened surface. On section, the cortex may be seen to be thinned and the pyramids slightly atrophied. The general appearance is pale grayish, sometimes mottled with areas of red, but hemorrhage is never prominent. Microscopically there are extensive glomerular lesions, largely proliferative, but many glomeruli are atrophied in varying degree. The tubules likewise show more atrophy than degeneration. The quantity of connective tissue is moderately increased. The blood-vessels are considerably thickened.

Symptoms and Physical Findings.—As in the subacute form, *edema* is the most striking symptom. It may be distributed in various parts of the body or confined almost solely to the subcutaneous tissues, or to one or several of the body cavities. In certain locations it is particularly annoying. Edema of the genitalia may hinder urination. The skin of the legs may burst and drain inconveniently, or become infected and cause much discomfort. Edema may close the eyes or, when it is in the retina, hinder vision.

Edema of the brain may cause symptoms of cerebral pressure; that of the lungs, the production of a profuse, frothy, watery sputum with dyspnea. In such cases the patient literally drowns. Edema of the gastro-intestinal tract may be responsible for many of such digestive disturbances as lack of appetite, gas, nausea, vomiting, constipation, or diarrhea. Subcutaneous edema may entirely obscure an extreme emaciation.

With edema there is malaise, lack of strength, digestive disturbances, sometimes headache. Blood-pressure is usually above normal and at times high. Cardiac and vascular disturbances are not prominent in the earlier periods; later they may become marked. Anemia appears in the later stages, but, as a rule, is slight even though the patient has all of the appearance of a marked reduction in hemoglobin and red cell count. In some patients edema gradually disappears and the condition slowly shifts to a chronic nephritis without edema. This disturbance lasts longer than when the edema persists.

The urine, which is decreased in amount, is of normal or increased specific gravity. Its sodium chlorid content is below normal. Albumin is abundant. Casts are usually of the hyaline type. Leukocytes are infrequent and red cells rare. The phenolsulphonephthalein excretion, which is at first slightly decreased, continues to diminish gradually, while the blood nitrogen values slowly increase from normal to moderately elevated figures. Usually these evidences point to quite a fair renal function even when the kidney excretes sodium chlorid and water very poorly. Blood chlorids are moderately increased, but there is no close parallelism between the level of chlorids in the blood, their excretion in the urine, and the occurrence of edema. Uremia is infrequent, but may occur. Exudate and hemorrhage into the retina are less common than in chronic nephritis without edema.

Diagnosis presents little difficulty, but this type of nephritis may be confused with other conditions, as is pointed out in the discussion of the subacute form.

Prognosis is bad. In the earlier stages, prognosis is usually quite out of proportion to the results of tests of renal function, such as phthalein excretion and blood nitrogen values, for these may be but slightly changed. Gradually the phthalein excretion falls and the blood nitrogen increases, changes which point to a progression of the renal process.

Treatment.—The edema is the chief feature of this disturbance which requires treatment and should be controlled by the measures employed for subacute nephritis. In addition, there should be more effort to maintain an adequate and properly balanced diet than in the acute and subacute forms. Much consideration must be given to the peculiarities of the patient's appetite, and the theoretical fitness of diet loses its value when the patient fails to eat; any food willingly taken may be more helpful than one accepted grudgingly, even if not adapted to the requirements of a kidney excreting sodium chlorid very ineffectually.

If anemia develops, iron should be given. The old-fashioned preparations, either Blaud's pills (*pilulæ ferri carbonatis*), one three times a day, or Basham's mixture (*liquor ferri et ammoniæ acetatis*), 15 to 20 c.c. three times a day, are fully as good as any of the newer forms.

Chronic Nephritis without Edema.—Chronic nephritis without edema is by far the most frequent form of chronic nephritis. A common term for it is "*chronic interstitial nephritis*," an excellent term for a prominent

part of its pathological picture; as the overgrowth of interstitial tissue is, however, probably only a secondary change, this term is unsatisfactory. In this form of nephritis cardiovascular disturbances are intimately interwoven with the renal changes and the disease is more properly a cardiovascular-renal disturbance than a nephritis. In the great majority of cases the blood-pressure is high.

Pathology.—In this type of nephritis the kidney is typically small, red, and granular, with an adherent capsule and thinned cortex. Connective tissue is increased in amount, most markedly in bands enclosing atrophied glomeruli and tubules, with intervening portions where connective tissue is less prominent and renal structures fairly normal. It is generally believed that this connective-tissue proliferation is secondary either to the antecedent proliferative and degenerative changes in glomeruli and tubules, or to the vascular lesions which disturb the nutrition of the actively functioning kidney structures.

Many of the *glomeruli* in such a kidney show changes, largely atrophic in type, and the same is true of the epithelium lining the tubules. Sometimes in areas where the connective tissue has not increased, the tubules are tortuous, moderately dilated, and lined by epithelial cells higher than normal; connected glomeruli may be enlarged. Although such changes are regarded as compensatory hypertrophy there is, nevertheless, actually a marked reduction in the functioning elements of such a kidney.

Blood-vessels almost always undergo such changes as thickening of the wall and reduction of the lumen. Very often the thickening is patchy and encroaches upon the lumen irregularly. Thrombosis is often seen. Various degenerative as well as proliferative changes appear in the vessels.

Symptoms and Physical Signs.—The symptoms vary greatly. Often they are very indefinite, hardly more than a sense of reduced well-being. When more marked they may be associated with inefficient renal function or be caused by secondary or associated hypertension, arteriosclerosis, and cardiac disturbance. It is in this form of nephritis that an examination of the eye-grounds by an ophthalmologist may reveal for the first time evidence of a probable nephritis, or that an examination for life insurance demonstrates unexpected albuminuria and hypertension. An attack of uremia or a cerebral hemorrhage may be the first warning of the existence of the disease.

The disturbance occurs for the most part in patients of more than forty years of age, but cases do occur at all ages with a decreasing frequency down to early childhood. The disease in children may result in dwarfism. The actual beginning of chronic nephritis without edema is nearly always insidious and the actual onset is rarely recognized. Progression may be fairly rapid or extremely slow.

Early evidences of chronic nephritis of this type are loss of weight, lack of strength, a decrease in energy and initiative, a growing nervousness or irritability, and slowly increasing nocturia. Such digestive disturbances as loss of appetite, bad taste in the mouth, sense of gastric fulness or weight, and flatulence are quite common. These may be corrected by catharsis, only to reappear. Headache, fulness in the head, dizziness, lack of concentration, cerebral irritability, and the like may be early or late symptoms, and result from associated cerebral vascular disorder.

Cardiovascular disturbances are common and sooner or later develop in nearly every case. The blood-pressure is almost always increased; and

high figures, 250 mm. of Hg systolic pressure or even higher, with a corresponding increase in the diastolic pressure, are common. Blood-vessels usually show demonstrable changes; the wall is moderately thickened and the vessels are lengthened so as to become more or less tortuous; sometimes there are marked evidences of arteriosclerosis with or without calcification. It is well to remember, however, that a radial artery may feel soft and easily compressible when the blood-pressure is actually high. It is well to inspect and palpate radial, brachial, temporal, carotid, and femoral arteries in order to obtain an idea of the condition of the general arterial system.

Hemorrhages occur as a result of vascular lesions plus hypertension. Epistaxis is frequent and difficult to control, and may be the first warning of chronic nephritis. Hemoptysis may be due to the vascular changes. Retinal and cerebral hemorrhages are especially common. Hematuria may occur as a result of renal hemorrhage.

Sooner or later *cardiac hypertrophy* can be detected, but even with marked hypertension it may long remain very slight. Gradually evidences of cardiac insufficiency appear with dyspnea, edema, and chronic passive congestion of the viscera. Very often the symptoms of cardiac failure dominate the clinical picture and the renal lesion is overlooked. The edema of cardiac failure may be mistaken for a renal edema, and the condition at this stage be wrongly diagnosed as nephritis with edema rather than as circulatory edema with chronic nephritis.

As time goes on, the heart may become very large, develop an apical thrill and murmur suggestive of mitral stenosis, show a basal diastolic murmur due to dilatation of the aortic or pulmonic ring, or present an arhythmia, either extrasystoles or auricular fibrillation. With extrasystoles the patient may complain of palpitation. Pulsus alternans may be encountered; in some patients it is marked enough to be detected by palpation, while in others it can only be demonstrated by the auscultatory method of blood-pressure determinations or by polygraphic tracings. With these changes there may be precordial discomfort or angina-like pains; very often true angina occurs. The electrocardiogram, besides demonstrating extrasystoles, fibrillation, and other types of arhythmia, may show evidence of myocardial disturbances in the changed form of the ventricular complex.

Dyspnea often develops. Particularly distressing is the paroxysmal dyspnea, often coming at night, sometimes as a totally unexpected and very alarming symptom, which may not recur for several weeks or may return with great frequency and be wrongly diagnosed as bronchial asthma, the underlying nephritis being entirely overlooked. The Cheyne-Stokes' type of respiration often appears in the later stages with or without marked signs of circulatory failure.

In patients with chronic nephritis without edema the *skin* is frequently dry with a pronounced tendency to eczema. Pruritus may be most distressing. Many of these patients have a very characteristic appearance with cachectic pallor or even fairly marked yellowish or brownish pigmentation and a progressing secondary type of anemia. The blood-picture is that of a secondary anemia; when this is marked there is some leukopenia. The anemia results from some toxic process and has no relation to hematuria. Curiously, anemia is most pronounced in this form of nephritis in which blood is very rarely present in the urine and is but slightly marked in types of nephritis with persisting hematuria.

Patients often complain of black specks before their eyes, flashes of light, scintillating scotomata, dimness of vision, or transitory blindness. Ophthalmoscopic examination is very important, for it allows judgment of the condition of small blood-vessels inaccessible to other modes of examination. Changes in the vessels themselves, retinal hemorrhages and exudate, and slight edema of the optic disk may be found. Retinal changes are very common in this type of nephritis. All of these emphasize the very important fact that the disease is wide-spread and involves smaller blood-vessels in many parts of the body.

In chronic nephritis without edema the *urine* is usually pale, increased in amount, of low specific gravity, and contains small amounts of albumin and a few casts, chiefly hyaline, with a very few finely granular casts. There is, as a rule, an increase in frequency of urination, especially at night, and a lag in excretion, so that the quantity passed at night is proportionately increased. If the urine is collected at two-hour intervals during the day, and in a single twelve-hour nocturnal interval, there may be seen a decreased variation in specific gravity from specimen to specimen as contrasted with the normal variation of ten or more points, a general lowering of the specific gravity for all specimens, and an increase in the quantity passed at night. These changes are found when renal function as measured by phthalein excretion and blood nitrogen determinations is quite good; later the phthalein excretion falls to a trace or zero and blood nitrogen mounts to a high level; often this occurs abruptly. These determinations are useful measures of renal function, especially when repeated at intervals. A single test is subject to errors in the technic; repetition serves as a check on errors and also provides a curve which indicates the rate of progression of the disease. Small traces of glucose are not uncommonly encountered, but it is rare for these to be of any great significance as a diabetic phenomenon. Periodically there may be hematuria, but for the most part red blood-cells are not found in the urine sediment.

In chronic nephritis slight degrees of *acidosis* develop as renal function falls. As a rule the urine is more acid than normal. In advanced nephritis acidosis becomes more marked and in the late stages there may be air hunger with lowered CO_2 tension of blood and alveolar air. Sodium bicarbonate therapy may relieve these symptoms, but there is no real benefit to the patient so far as progress of the disease is concerned.

The *basal metabolism* of some patients is moderately increased during the course of chronic nephritis without edema; while in the type with edema it may be decreased.

This is the type of nephritis in which *uremia* is most often encountered. The most significant evidences of uremia are drowsiness, increasing headache, sleeplessness, muscular twitchings, tonic or clonic spasms, convulsive seizures, and coma. These may develop suddenly or gradually. It is very unsafe, however, to diagnose such symptoms as uremic manifestations unless the phthalein excretion is low and the blood nitrogen high. Without these findings convulsive seizures and coma are usually the result of cerebral hemorrhage, epilepsy, arteriosclerosis, or brain tumor. The urine of a patient with any sort of convulsive seizure or coma is apt to contain albumin and a few casts. These are the findings in many cases of uremia. Unless the renal function is demonstrably low (phthalein test or blood nitrogen determination) one should be skeptical of the diagnosis of uremia until a

thorough autopsy has revealed definite disease of the kidney and no local cerebral lesion to account for the symptoms. Many conditions diagnosed as uremia on the basis of toxic manifestations and the presence of albumin and casts in the urine, prove at autopsy not to be caused by nephritis or to be associated with nephritic lesions too slight to produce uremia.

With the onset of the nervous symptoms of uremia, *nausea* and *vomiting* often occur. As they may appear in a patient previously in normal condition and progress rapidly to a fatal outcome, such conditions are often reported by the newspapers as fatal acute indigestion.

Diagnosis.—In chronic nephritis without edema the diagnosis is usually easy except in the earlier stages. When there are no other detectable changes than a small trace of albumin and an occasional cast in the urine, the diagnosis must depend on a somewhat prolonged observation to determine the persistence of the urinary changes and the presence of some of the signs and symptoms just described. As most patients have an elevated blood-pressure, it becomes important to distinguish their condition from so-called *essential hypertension* in which there is little or no evidence of disturbance of renal function. If hypertension is present and the renal function is definitely decreased, as measured by the tests described above, it seems reasonable to assume that there is a close relationship between the renal lesion and high blood-pressure. When the urine is almost normal and renal function tests are normal, the diagnosis of essential hypertension is justified. Hypertension alone should not be considered evidence of chronic nephritis.

Uremia, when renal function is much decreased, can usually be diagnosed from the symptoms. When the phthalein output is only moderately decreased and blood nitrogen values are but moderately increased, any sudden convulsive seizure, coma, or intense headache is very apt to be due to an organic cerebral lesion, most often to hemorrhage, occasionally to tumor, and should not be explained on the basis of uremia. It is to be remembered that the urine of patients with all sorts of cerebral seizures is apt to contain some albumin and casts even though the kidneys are structurally normal, and so the urinary findings just after a seizure may be misleading.

When ophthalmoscopic examination shows retinal hemorrhage, edema, some variety of exudate, or white spots, vascular lesions may accompany nephritis, but these in themselves do not justify a diagnosis of nephritis without other evidence.

Prognosis.—Patients with chronic nephritis without edema do not recover. The duration of the disease varies from months to many years. In other words, in some cases the disease progresses steadily and rather rapidly, while in others it advances with extreme slowness. Repeated tests of renal function, using the two-hour renal test for mild signs and the phthalein and blood nitrogen determinations for the more severe, are of great service in determining prognosis because they, best of all, give an idea as to changes in the actual renal process. They must, of course, be evaluated in relation to variations in urinary albumin, casts, red cells, and leukocytes. Sometimes, however, a patient with very low renal function may continue to live for several years. A progressively increasing anemia is also valuable as a prognostic index of seriously progressing diseases. Similarly, a declining body weight, if the patient is not living on a diet of subnormal caloric value, indicates progression of the renal lesion, and hence is a bad prognostic sign.

Since in this group of patients downward progress may be manifested by increasing circulatory disability as well as by decreasing renal function, cardiac efficiency, as evidenced by symptoms and signs of circulatory failure, has to be taken into account in measuring prognosis.

Sudden vascular accidents, particularly cerebral hemorrhage, may change unexpectedly and completely the prognosis that has been given for any individual patient. Evidences of arteriosclerosis in the eye-grounds, particularly when associated with general hypertension and the presence of foci of hemorrhage in the retina, add to the probability of a cerebral seizure as an interruption in the otherwise steady and slow progression of the disease.

Treatment.—In treatment, consideration must be given to the kidney, the heart, and the peripheral blood-vessels. Definite foci of infection need to be eradicated as possible causes of progression in all of these systems, but the indiscriminate removal of slightly diseased or practically normal teeth and tonsils has no justification. The disturbing effects of operative measures must be taken into account, and tonsillectomy, certainly in adults, is to be regarded as a major operation from which the patient recovers only after weeks.

A warm, equable *climate*, free from great extremes of temperature and moisture, is desirable for the chronic nephritic. With hypertension high altitudes are undesirable, particularly when some signs of circulatory insufficiency exist. Physical and mental stresses and strains are to be curbed. Judicious exercise in the open air proportioned to the patient's strength and circulatory condition is very desirable. Golf, horseback riding, and walking are often valuable therapeutic measures if they do not produce fatigue which persists.

There is no *medicinal therapy* for the renal condition. Diuretics are undesirable. Treatment for the condition of the circulation should be based on the principles suited to cardiac insufficiency; the proper use of rest, exercise, and digitalis may greatly influence the condition of the patient. For hypertension, medicines are of no real service. For this, regulation of the stresses and strain of life and proper dieting is all that can be offered. An extreme reduction of the salt intake does not seem to be of great help in reducing blood-pressure.

Diet is the keynote of the management of chronic nephritis without edema, and yet limitations in the food intake are based largely on empirical data. Such evidence as there is indicates the use of a diet somewhat restricted in protein content, much limited as to sodium chlorid content, and containing an average of 1500 to 1800 c.c. of fluid per day. If the patient has edema the fluid should be further restricted. The patient with mild symptoms should receive daily from 60 to 75 gm. of protein, while in more advanced cases the amount should be reduced to 40 gm., and later to 25 gm. Total non-protein nitrogen or urea-nitrogen determinations in the blood are extremely valuable in planning the patient's diet so far as protein is concerned. When the quantity of these in the blood is above normal the protein content of the food should be lowered; when normal or slightly below normal the protein intake should be increased accordingly. This type of dietary régime is suited to both the renal disturbance and the hypertension. As the disease is chronic, any diet to be suitable for continued use must have a sufficient caloric value (2500 cal. or more), and must be appetizing. Any diet which is prescribed must be eaten; when the patient declines to

eat, every effort must be made to shift the diet so as to remove the objectionable features. If the patient begins to vomit, every effort must be concentrated on getting into the patient food of any sort that will be retained in order to decrease the breakdown of body proteins. To permit any considerable undernutrition is more serious than to give foods theoretically undesirable.

The following food list, devised by O'Hare, has proved very useful in the management of nephritis.

Nephritic Diet

Any combination of the foods listed below may be selected.
Foods not listed below must not be taken.
In Groups I and II there is a restriction in the total amount.
The foods in these groups must be served in full or half portions.
A full portion in Group I counts 1.
A full portion in Group II counts 2.
In Group III the quantity of each is not restricted, altho you are urged to use discretion.

YOUR TOTAL SCORE FOR THE DAY SHOULD BE.....*

YOUR TOTAL AMOUNT OF FLUID SHOULD BE.....PINTS.

Do not add salt or spices to the food after it has been cooked.

GROUP I.
(Each full portion counts 1.)

	Full Portion	VEGETABLES, Etc.	Full Portion
Bread (white)	1 av. slice	Baked beans	1 tbsp.
Bread (graham)	1 av. slice	Lima beans	1½ tbsp.
Uneeda biscuit	5 crackers	Potato, creamed	1 tbsp.
Shredded Wheat	1 biscuit	Potato, mashed	1½ tbsp.
Graham crackers	5 crackers	Potato, baked	1½ med.
CEREALS, Etc.		Potato, boiled	1½ med.
Oatmeal	2 tbsp.	Canned corn	2½ tbsp.
Boiled rice	3 tbsp.	Green peas	2 tbsp.
Cornmeal mush	4 tbsp.	Beets	5 tbsp.
Cream of Wheat	6 tbsp.	Spinach	4 tbsp.
Farina	6 tbsp.	Bananas	2 large
Macaroni	4½ tbsp.	Cream, heavy	¾ cup

GROUP II.
(Each full portion counts 2.)

	Full Portion	FISH	Full Portion
Milk	1 glass	Cod, boiled	1″ x 1″ x 1½″
Egg	1 egg	Haddock, boiled	1″ x 1″ x 1½″
Eggs (scrambled)	1½ tbsp.	Halibut, boiled	1″ x 1″ x 1½″
Flour, sifted	¾ cup	Mackerel, boiled	1″ x 1″ x 1½″
MEATS		Salmon, boiled	1″ x 1″ x 1½″
Lamb chop, broiled	¾ chop	Smelt	½″ x 1″ x 3″
Lamb, roast	3″ x 2½″ x ¼″	Oysters	7 oysters
Beef, roast	3″ x 2″ x ¼″	Crabmeat, canned	2 tbsp.
Beef steak, broiled	2″ x 1″ x 1″	Salmon, canned	1½ tbsp.
Chicken, roast	3″ x 3″ x ⅛″	Shrimp, canned	6 small

GROUP III.
(No restriction.)

VEGETABLES		FRUIT		MISCELLANEOUS	
Asparagus	Mushrooms	Apple	Orange	Sugar	Cornstarch
Cabbage	String beans	Apricot	Peaches	Maple Sugar	Arrowroot
Carrots	Tomato (fresh)	Blueberries	Pears	Syrup	Tapioca
Cauliflower	Tomato (cooked)	Cherries	Pineapple	Honey	Post-Toasties
Celery	Onions	Cranberries	Plums	Candy	Butter
Cucumbers	Squash	Grapefruit	Prunes	4 dates per day	Olive Oil
Lettuce	Turnips	Grapes	Raspberries	3 Sunshine arrowroot cookies per day.	
		Muskmelon	Strawberries		
		Lemons	Watermelon		

*Each point in the score equals 4 grams of protein; *e. g.*, a score of 7 equals 28 grams of protein.

Tea and coffee are best limited in amount, but need not be entirely omitted. Condiments, spices, and alcoholic beverages are to be avoided. The use of tobacco should be restricted, but not necessarily prohibited.

Constipation must be avoided. For many patients a watery catharsis

once or twice a month is beneficial. A weekly sweat bath, when not debilitating to the patient, is beneficial. The electric light form is the best.

If uremia develops in a plethoric type of patient or in one without anemia, 300 to 500 c.c. of blood should be removed by puncture of a vein, but as uremia often develops in the anemic, bleeding is frequently contraindicated. Watery catharsis is then preferable. Sweating is rarely of any use except in low-grade chronic uremia because it is too debilitating, and a good response does not often come until after several daily sweat baths have been given.

Though there is an admitted pessimism as to the results of treatment of nephritis, both subacute and chronic, still the judicious regulation of the lives of these patients with respect to physical and mental activities, diet, etc., and treatment of the various incidents of the disease as they arise, does accomplish much for the comfort of the patients and prolongs their period of reasonable activity.

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MALFORMATIONS OF THE KIDNEY

The metanephros, or permanent kidney, develops from two portions of the Wolffian system. Starting from the pelvic region of the embryo the two kidneys migrate upward toward the head until they attain the normal position at the lower margin of the thorax. At first the renal pelves are directed forward, but as a result of rotation they finally face each other. The permanent blood-supply is not acquired until the kidneys reach their final position; hence the arteries usually arise from the aorta at the normal level of the kidney, or, exceptionally, from any large vessel at the level where the kidney happens to stop migrating. The secreting tissue and the collecting tubules arise from different layers in the Wolffian system, and subsequently unite to form a channel between the lumen of the secreting cells and the collecting system. Should this union fail to take place, the pressure under which the urine is secreted causes the formation of cysts.

This is the mechanism ordinarily held to be responsible for the formation of cysts in the disease known as *cystic degeneration of the kidney*. Although probably the most important of the anomalies of development, there is still some discussion as to the origin of this disease, and for this reason it is described below in the section on Cysts.

Other anomalies may be classified by their relation to the number, position, blood-supply, and form of the kidney. *Supernumerary kidney* is exceedingly rare. On the other hand, *congenital absence of one kidney* is

observed once in about 2000 autopsies, and has caused the death of more than one patient after the removal of the only kidney. It is more common in males than in females. It is the left kidney which is most frequently missing. The single kidney is hypertrophied, and, consequently, this condition should always arouse suspicion of solitary kidney. A *misplaced* kidney is seen about twice as frequently, and may be distinguished from movable or floating kidney in that it has never reached the normal position, is fixed in place, lacks the long mesenteric attachment, and is usually on the left side. It is commonly found in the true pelvis or near the promontory of the sacrum. In pregnant women such a kidney may suffer damage by pressure or interfere with parturition. When a tumor low in the abdomen is associated either with renal symptoms or with dystocia such misplacement should be suspected. Although more common in men, it causes symptoms less frequently than in women. The treatment is surgical, but since the misplaced organ tends to be solitary, especial caution is necessary in advising nephrectomy. Operative fixation at a higher level has been performed successfully. *Aberrant blood-vessels* are extremely common, but of surgical interest only, except when they cause hydronephrosis by pressure on the ureter.

Abnormalities of form are commonly produced either by persistence of the *fetal lobulations* or by fusion. Irregularities due to the former cause are of interest to surgeons because of their association with anomalies of the blood-vessels. Fusion is the result of union of the nephric buds of the two kidneys, and usually takes place at the lower poles, producing the "horseshoe kidney"; sometimes, however, it occurs at the upper poles. When the lower pole of one kidney unites with the upper pole of its fellow the "long" or "tandem kidney" is produced. The fusion tends to arrest migration before the kidney has attained its normal level. The condition may sometimes be suggested by palpation of a tumor across the midline which transmits the impulses of the aorta. Such kidneys are of no clinical importance except that they are perhaps more subject to obstruction, inflammation, or cystic degeneration.

When *one* or *both ureters are absent* the corresponding kidney atrophies. *Bifurcation* of the *ureter*, usually the left, occurs. There may even be *two separate pelves* in one kidney, with a double ureter extending all the way to the bladder, with a double opening. Another anomaly is *implantation* of the *ureter* in an *abnormal* position in the bladder, or outside of it. *Congenital stricture* of the ureter occurs.

Malformations in general tend to occur not singly, but in groups, so that when one is found, another should be suspected. They may be associated with such anomalies of the genital organs as undescended testicle.

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MOVABLE KIDNEY

(*Nephroptosis, Prolapsed Kidney, Floating Kidney*)

Definition.—A kidney is said to be movable when it is displaced enough to be palpable—a very common disorder. Normally the organ may move

between 1 and 2 inches; but in many cases the range of motion is far greater than this, with no other evidence of abnormality. The kidney is situated normally in the paravertebral fossa, with its upper portion overlying the twelfth rib. Its only support, apart from intra-abdominal pressure, is its bed of fatty areolar tissue, surrounded by a distinct fascia, everywhere closed except at the lower end. The fact that the paravertebral fossæ are shallower and more open at the lower end in women than in men may account in part for the greater prevalence of the disease in the female sex.

Etiology.—The causes of movable kidney include congenital predisposition, visceroptosis, anatomy as affected by sex, relaxation of the abdominal wall, loss of body fat, enlargement of the kidney, and trauma. Rarely the cause is frankly *congenital*, and the kidney, instead of remaining a retroperitoneal organ, swings free in the abdominal cavity, restricted only by the peritoneal attachment, or mesonephron, with which it is provided. For this anomaly the term *floating kidney* is most appropriate. In the ordinary type the occurrence of several instances of movable kidney in a single family speaks for a congenital factor, related possibly to local conditions in and about the kidney, but more probably to peculiarities of body form. Prolapse of the kidney is, in fact, often associated with a type of bodily configuration known as *habitus enteroptoticus*, *visceroptosis*, or *splanchnoptosis* (Glenard's disease). Persons so constituted are recognizable at a glance by the long chest, narrow costal angle, and the prominence of the lower abdomen. Since they are ordinarily very thin, the perirenal tissue is presumably deficient in fat; moreover, the renal fossæ are shallower and therefore offer less support to the kidney than in the ordinary individual. Thus in two ways the renal support is defective. Common though movable kidney is in individuals of this type, it may nevertheless occur when the bodily configuration is normal.

The fact that movable kidney is more common in *women* than in men, in the ratio of 10 : 1, is ascribed in part to anatomical differences, but more to the relaxation of the abdominal wall which follows child-bearing. Any growth or accumulation, such as pelvic tumor or ascites, which stretches the abdominal wall and is subsequently removed, has the same effect. Mere size plays a part, as with polycystic kidneys, which are often prolapsed. *Repeated trauma*, such as coughing or straining, has also been considered an etiological factor. Rapid loss of fat is still another cause.

Symptoms.—In the majority of cases symptoms are lacking. In a large group they are not directly referable to the kidney, but are multifarious and may be classified as dyspeptic or nervous. The *dyspeptic symptoms*, which are often associated with enteroptosis, have also been explained as of renal origin, either reflex or mechanical. In the latter case the kidney is thought to drag on the duodenum. The *nervous symptoms* are mainly neurasthenic, and may or may not be related to the displacement. The *pain*, which is one of the chief manifestations of the disease, is probably of renal origin. Some patients complain of feeling something loose inside, others of a sense of weight and weakness. The more severe types of pain are described as dull and dragging, or at times colicky. In general, the discomfort tends to be aggravated by standing or walking, and relieved by lying down. Outspoken colic is the result of twisting of the pedicle, with blocking of the veins or kinking of the ureter. The former causes acute congestion; the latter, intermittent hydronephrosis. The sudden closure

of the ureter produces a syndrome which in its characteristic form is known as *Dietl's crisis*. This consists of attacks of acute pain accompanied by nausea, vomiting, and the phenomena of shock, also by retention of urine and increase in the size of the kidney. The pain ceases abruptly, with the passage of large quantities of urine. The attack may be quite as severe as if caused by stone. The pain is usually referred to the kidney, but sometimes radiates down the course of the ureter. The renal enlargement is due to accumulation of urine in the hydronephrotic sac, which, owing to the intermittent nature of the obstruction, tends to be large, and may even fill the entire loin. Little urine is passed during an attack, but after a period varying from hours to days the obstruction is relieved and the urine gushes from the sac. Throughout there are few abnormal constituents in the urine; blood is rare, but albumen may be present for a short time after the attack.

The position of the kidney is determined bimanually, with the patient either standing or recumbent. If standing, the subject should lean forward slightly, resting the hands on some convenient support; in either case the examination is made by putting one hand on the loin, between the ribs and the pelvis, and the other on the abdomen. A palpable kidney is felt as a firm rounded mass descending on inspiration. In the more marked cases it may be caught and held down.

Diagnosis.—A floating kidney may be distinguished by its extreme motility, particularly in an upward direction, and by the peculiar sickening sensation experienced by the patient when it is compressed. The other types of nephroptosis are readily diagnosed by palpation. More important, however, than the detection of the misplacement is the question whether or not it is the cause of symptoms. The urinalysis is of little aid because blood is rarely present, and albuminuria transitory. When symptoms are of renal origin they disappear if the kidney is replaced, either by manipulation, posture, or other means. In like manner, symptoms which can be reproduced by injection of fluid into the ureter are probably renal in origin. So also are enlargement of the kidney or attacks of Dietl's crisis. When the latter syndrome occurs, it can be differentiated from stone by the frequency with which polyuria occurs after subsidence of the attack, and the rarity with which blood-corpuscles are found in the urine. *x*-Ray will usually reveal the stone if present. The degree of renal motility may be shown by pyelograms, *i. e.*, *x*-ray, of the renal pelvis taken when the patient is standing and again when recumbent.

Prognosis.—Little or no renal damage is to be expected except with hydronephrosis and its complications.

Treatment consists in the attempt to return the kidney to a more nearly normal position and hold it there. For this an increase in the adipose tissue of the patient, restoration of the normal pressure within the abdomen, or surgery, may be utilized. If the patient is thin the *diet* should be increased in the hope of adding to the perirenal fat and thereby restoring some of the normal support. Relaxation of the abdominal wall may be treated by *exercises* designated to strengthen the abdominal muscles, and an abdominal corset often gives relief. Patients suffering from nervous or dyspeptic symptoms should receive appropriate treatment. Neurasthenia is often the most important element in the case. Surgery, though often beneficial, is uncertain in its results and should only be considered in severe or persistent

cases, or when there is a definite pathological lesion. Indications for operative treatment are the presence of severe symptoms; intermittent hydronephrosis accompanied by permanent dilatation of the renal pelvis; bleeding; or renal complications. Operation is designed to replace the kidney and hold it in position.

HENRY B. RICHARDSON.

CIRCULATORY DISTURBANCES

Definition.—Disturbances of the renal circulation to be considered here are due to circulatory changes other than hypertension and arteriosclerosis.

Etiology.—Since the nervous system affects the kidney for the most part indirectly, through innervation of the blood-vessels, almost any nervous influence acting on this organ is, in a sense, a circulatory disturbance. The excretion of urine depends on the rate of flow of the blood, and to a less extent on the blood-pressure. Experimental blocking of the flow of blood causes a diminished secretion, or even anuria. Analogous to this clinically are the conditions which reduce the rate of blood-flow and thereby cause chronic passive congestion of the kidneys. The cause is either a defect in the circulation as a whole, as in myocardial insufficiency, or obstruction of the renal vein by thrombosis or pressure. Urinary secretion ceases when the blood-pressure falls below a certain level, which, however, does not occur except in extreme shock. Quite another form of circulatory disease is represented by *infarction*.

Symptoms.—The symptoms of chronic passive congestion are secondary to those of the causative disease, whether a general circulatory defect or a local obstruction. Subjectively, the only peculiarity which may be noticed is a decrease in the quantity of urine and an abnormally high color. Physical examination reveals only the associated cause. The *urine* is found to be scant, of high specific gravity, and of high color. Albumen is present in moderate amount; and the sediment contains hyaline and granular casts and red blood-corpuscles. The various functional tests give different results; thus the elimination of phenolphthalein is reduced to about half the normal, whereas there is no retention of nitrogenous products in the blood. In Mosenthal's two-hour test the specific gravity in the different specimens shows some fixation, but usually at a high level.

Diagnosis.—The diagnosis lies between this condition, which does not outlast the causative factor, and a moderate grade of permanent nephritis. In favor of congestion is the high specific gravity of the urine, the lack of nitrogen retention, and the absence of albuminuric retinitis. Hypertension is not a result of chronic passive congestion, and is absent more often than not. Christian has called attention to the fact that patients with chronic passive congestion respond to diuretics, whereas nephritics do not.

Prognosis.—The condition is not associated with permanent renal damage; at least the renal function outlasts the circulatory function.

Treatment.—The treatment is primarily that of the underlying cause.

The *Karell diet*, which limits the intake of fluid and food to 800 c.c. of milk in twenty-four hours, very often produces a striking diuresis. It has recently been suggested that this may be due to the high calcium content of the milk. *Diuretics*, in particular *theocin*, produce a most striking increase in the amount of urine secreted.

Infarcts of the kidney are lesions caused by the lodgment of emboli in arteries within the kidney. Symptoms are often lacking, or overshadowed by those of the acute infection or endocarditis from which the embolus is derived; when they do occur, they consist of a sharp pain in the flank, often followed by the appearance of red blood-cells, albumen, and a few leukocytes in the urine. The kidney may in some cases be tender. There is no special treatment, and the prognosis is good as far as it applies to the kidney, except when the embolus is large enough to block the main trunk of the renal artery.

HENRY B. RICHARDSON.

AMYLOID DISEASE OF THE KIDNEY

Amyloid takes its name from the fact that it resembles starch in the color of its reaction to iodin. It is deposited in certain organs in the course of wasting disease, such as tuberculosis or prolonged suppuration, especially of the bones. In the kidneys this substance, which is deposited first in the small vessels and glomeruli, may increase until it destroys the tissues. It is laid down also about the tubules, and may cause the disappearance of the epithelial cells. With iodin it stains a walnut or mahogany brown color. The deposit is not peculiar to the kidney, but is found in the liver and spleen as well, in quantities sufficient to cause enlargement. It produces a chronic nephritis, the symptoms of which present nothing characteristic of amyloid. The diagnosis of the latter depends on the signs of wasting disease, together with enlargement of the liver and spleen. The disease may progress until the renal function is extremely impaired. In the treatment the constitutional disease is attacked, and the nephritis treated as if of other origin. The prognosis depends mainly upon the associated condition.

HENRY B. RICHARDSON.

INFECTIONS OF THE KIDNEY

(*Excluding Tuberculosis*)

Definition.—The term "*infection of the kidney*" is here used to describe diseases due to the actual presence of bacteria in the kidney, its pelvis, or the perirenal tissue. It is thus distinct from the nephritis due to bacterial

or other toxins originating elsewhere in the body. The definition of the various forms of this disease appears in a subsequent paragraph on pathology.

Etiology.—The etiology includes the nature of the infecting organisms, their origin in the body, the route by which they arrive in the kidney, and the conditions which predispose them to lodge and set up inflammation. Exclusive of the *tubercle bacillus*, the two most important types of bacteria are: first, the group of the *Bacillus coli;* and second, the pyogenic cocci. The *Bacillus coli* is the cause of over three-fourths of the cases. It has a tendency to involve the pelvis of the kidney to a greater extent than the parenchyma and is also distinguished by its inability to produce ammonia or render the urine alkaline. This organism has a reputation for remarkable tenacity. The pyogenic cocci include the *Staphylococcus aureus* and *albus*, the *Streptococcus*, and the *Pneumococcus*. The *Gonococcus* is so rare in this situation as to be almost a medical curiosity. The *Streptococcus viridans* produces, usually in cases of bacterial endocarditis, peculiar lesions characterized by the presence of emboli in the arteries at the edge of the glomeruli, and by the formation of thrombi and subsequent sclerosis. Unlike the colon group, the pyogenic cocci in general tend to infect the parenchyma of the kidney and to produce perinephritic abscesses; unlike it also, they change the urea of the urine into ammonia, often making the reaction alkaline. They seem to be less pertinaceous than the colon group. Organisms of both types vary greatly in virulence. Many other infecting agents have been isolated, among them the *Bacillus pyocyaneus*, *Bacillus influenza*, and *Actinomyces bovis*. The *Treponema pallidum* of syphilis is found in the kidney, but is under dispute as a cause of inflammation.

Infections of the kidney are classified as descending or ascending, according as the focus of origin is outside or within the urinary tract. The distinction was formerly based on the idea that infections in the lower urinary tract could extend by direct continuity upward along the lumen. Experimental work has shown that this mechanism is rare. The so-called ascending infection passes either by way of the lymphatics about the ureter, or by way of the blood-stream, the weight of opinion being in favor of the latter. Whatever the path, it is certain that the colon bacillus starts in the lower tract and arrives at the kidney often enough to be responsible for the great majority of the renal infections. Another mechanism of infection, direct extension from neighboring organs, is rare, but does occur.

Since certain organisms, notably the typhoid bacillus, may pass through the kidney without causing any apparent harm, it is evident that bacteria can set up inflammation only under special conditions. This is possible if there is an increase in the number and virulence of the organism, or a decrease in the resistance of the kidney produced by local conditions. Among the latter, hydronephrosis and stone are notorious, probably because of stasis. Trauma of varying degrees of severity is another probable factor. Congestion and the irritation produced by bacterial and other poisons have also been blamed, as well as the ordinary type of toxic nephritis.

The incidence of the disease in relation to *age* and *sex* is influenced by the causative organism. Ascending infection by the colon bacillus is responsible for many cases in young girls, pregnant women, and in elderly men.

Morbid Anatomy.—When the infection is part of a general pyemia or septicemia both kidneys are found to be studded with small abscesses.

Other acute infections of the renal parenchyma may be grouped under the name of *focal suppurative nephritis.* In the milder form, the lesion consists merely of acute degeneration and congestion of the whole parenchyma, but in more advanced cases, areas of localized degeneration and necrosis are found in various parts of the renal tissue. When the infecting organism is the *Bacillus coli,* the initial lesions are chiefly in the medulla near the renal pelvis. By lymphatic absorption they spread radially, with the formation of the characteristic wedge-shaped areas of suppuration, and extend until they become visible through the capsule. Unless resolution takes place the abscesses increase in size, coalesce, and rupture into the renal pelvis, the perirenal tissue, or the blood-stream.

Acute pyelitis, as the name implies, affects mainly the renal pelvis. Few cases are observed pathologically. Keyes describes one in which the membrane of the pelvis was scarlet in color and thickened, and the parenchyma, although normal to the naked eye, showed under the microscope scattered patches of necrosis and round-cell inflammation. The chronic form of this disease is spoken of not as pyelitis, but as *chronic pyelonephritis,* to indicate that the pathological process has spread to the parenchyma. The early lesions are about the tubules, and consist of an infiltration with round cells, which sometimes breaks down into abscesses, and in any case ends with the formation of scar tissue. As a result the tubules are distorted, compressed, or destroyed. When the disease is chronic the gross pathology resembles that of chronic nephritis, in that the capsule is adherent, the normal markings lost, and the parenchyma thinned. In addition, the calyces are dilated, the walls of the pelvis thickened, and scars of old suppuration are found in the renal tissue.

The term *"pyonephrosis"* is best reserved for a condition in which the kidney is essentially a sac of pus bounded by the renal pelvis and a thin shell of sclerotic parenchyma.

Perinephritis is of two types. The first consists in the formation of connective tissue and may be found in greater or less degree in any renal infection. Since the perirenal fat becomes enmeshed in the scar, the lesion has received the name of *fibrolipomatous nephritis.* It is only the second type of perinephritis, however, which causes symptoms. This is manifested by the growth of an abscess which tends to spread like suppuration elsewhere, and may extend down the course of the ureter, or upward into the pleural cavity to set up an empyema. In most cases abscesses can be demonstrated in the renal cortex, although in some instances no such lesion can be found. The morbid anatomy differs little from that of suppuration which arises in adjoining viscera, such as liver, pleura, bowel, or spine, and extends by continuity to the perirenal tissue. For this the term *"retroperitoneal abscess"* is, however, more appropriate.

Symptoms.—The symptoms and signs of infection of the kidney are chills, fever, and leukocytosis; pain and tenderness in the kidney; the presence of bacteria, pus, and albumen in the urine; frequent and painful urination; and renal impairment. They may be classified as follows: (1) the constitutional reaction; (2) the local effects of stretching the capsule; (3) disturbances of urination; (4) abnormalities of the urine; and (5) signs of renal impairment. The *constitutional reaction* may vary from a brief rise of temperature to a fulminating sepsis. In the more severe cases there is a chill either at the outset or later. Leukocytosis, though not constant,

is usually present. The *stretching of the capsule* is sufficient, as a rule, to cause symptoms; when mild, a tenderness over the kidney which may be elicited by pressure, and when severe, spontaneous pain as well. This is localized in the loin usually as far back as the costovertebral angle, sometimes anteriorly in the region of the gall-bladder, or even as low as the appendix. If severe and high up, it radiates across the abdomen. Frequent and painful *urination* is common, whether as the result of reflexes from the renal pelvis or of infection of the ureter. Bacteria may nearly always be found in the urine and are significant provided that contamination can be avoided. This is best accomplished by catheterization. The organisms may be abundant without other abnormal findings, but whenever there is an actual abscess cavity communicating with the renal pelvis, *pus* is present in the urine. Conversely, pus in the urine in amount sufficient to form a sediment almost always comes from the kidney. In general, the further the lesion from the pelvis of the kidney, and the more acute the infection, the less the likelihood of pyuria, for it is obvious that unless there is a communication of some sort between the abscess and the collecting system, no pus can reach the urine. *Albumen* is even more constant than pus, but is less characteristic, because of the multiplicity of conditions in which it appears. It is ascribed not to the presence of the leukocytes, but to the renal irritation which accompanies every infection of the kidney. *Casts* are characteristically absent, a point upon which Keyes lays much stress. *Red blood-corpuscles* are rarely abundant enough to cause gross hematuria, but may commonly be detected under the microscope. The urine is scant and high-colored in the acute cases on account of bilateral involvement or reflex congestion of the opposite kidney; but may be increased in amount and of low specific gravity in the more chronic cases in which there is renal involvement.

The sole evidence of renal damage may be the albuminuria. On the other hand, all grades of functional impairment may be encountered, as demonstrated by the depression of the specific gravity, with fixation at a low level, and increase in the volume of the night urine; decreased elimination of phenolphthalein; and accumulation of nitrogenous waste-products in the blood. *Hypertension* occurs as the result of an associated toxic nephritis, or in advanced years as a coincidence. There may be more or less *edema*. Often in chronic cases the damage is sufficient to cause symptoms of *uremia*, such as loss of appetite, dryness, and a red glazed appearance of the tongue; headache; occasionally dizziness; perhaps decrease in the volume of the urine; hiccup; stupor; mental aberration, confusion; and eventually coma. These manifestations do not differ essentially from those of renal insufficiency due to other causes.

Special Types.—Among the special types of renal infection may be mentioned *urethral chill*, which occurs immediately after the first urination following the passage of an instrument through the urethra. It is now almost universally attributed to bacteria which are dislodged by the instrument and infect the kidney by way of the blood-stream. Accompanying the chill is a sudden high fever which subsides rapidly, but may occasionally be followed for a day or two by a slight irregular rise of temperature or even initiate a general septicemia. Factors said to be essential for the occurrence of the chill are chronic prostatitis, renal damage, and usually retention of urine.

Other acute renal infections are *pyelitis*, *pyelonephritis*, and *focal suppura-*

tive nephritis, which may be grouped together, since they cannot be distinguished clinically. When mild these cause a brief rise of temperature, and the appearance of pus, bacteria, and albumen in the urine. There is little or no spontaneous pain, but the kidney is tender, and possibly enlarged. In the severe form there is considerable fever. Pain and aching in the loin may be severe or absent, but according to Keyes tenderness may always be elicited by ballottement of the kidney. The procedure is the same as in palpating for movable kidney, but when the abdominal hand is as deep as possible, the kidney is sharply struck from behind, giving rise to the sensation of ballottement. The fulminating type is characterized by repeated chills and high temperature. Urinalysis often reveals little except the presence of albumen and a few red corpuscles, findings not characteristic enough to be of any great help. Diagnosis is made by tenderness in the loin, and depressed function of the affected kidney as shown by catheterization of the ureter.

The converse of the fulminating disturbance is chronic *pyelonephritis*, in which the febrile symptoms are, for the most part, lacking. The infection is not severe enough to distend the kidney or suppress urine. Urinalysis reveals pus, albumen, and bacteria. Reflex bladder symptoms are present, though variable. From time to time acute renal infection takes place, and ultimately, perhaps, a general septicemia. The renal function is impaired, sometimes to the point of definite toxemia or even uremia.

Pyonephrosis is the accumulation of pus in the renal pelvis with distention of the kidney. In severe cases this organ is reduced to a thin sac containing a large abscess. The symptoms are due to the size of the tumor, the presence of infection, and the damage to the parenchyma. The tumor usually causes local pain, tenderness, and marked enlargement. The infection causes the symptoms of sepsis and the appearance of pus and bacteria in the urine; while the renal involvement causes the same symptoms as when due to other causes. Typically, patients have a large, painful, tender tumor in the loin and a septic fever, but both the subjective symptoms and the enlargement may be so slight that the renal origin of the fever is overlooked. Ordinarily either the sepsis or the symptoms of renal toxemia predominate. The diagnosis is confirmed by ureteral catheterization, which demonstrates the renal origin of the pus, and the impairment of the function of the kidney.

Perinephritis is an extension of the renal inflammation into the surrounding tissue. When the lesion consists merely in the formation of scar it produces no symptoms. It is only the actual extension of the purulent process into the perirenal tissue which is of clinical importance. This condition is known as *perinephric* abscess. It is manifested by the symptoms of sepsis, and by the pain, tenderness, or sensation of mass resulting from the accumulation of pus. Both the acute and chronic types may begin with chill, fever, and leukocytosis, but the latter form often starts insidiously, with low fever. The pain tends to be diffuse, and, owing to the proximity of the diaphragm, increases on inspiration. The mass is frequently obscured by tenderness, or muscular rigidity, and may cause only a sense of resistance in front and behind. The occurrence of albumen and pus in the urine, and of renal impairment, depends on infection of the kidney itself. These signs are lacking more often than not and as a result the diagnosis often remains obscure until there is a palpable mass in the loin. Edema in the lumbar region makes the cause of the symptoms obvious.

Diagnosis.—Once the diagnosis of renal infection is entertained, it can be readily confirmed or disproved by special examinations. Perhaps the most important point, therefore, is the implication of the kidney as the source of trouble. Pus in the urine, unexplained fever, or obscure symptoms of renal toxicity should suffice to arouse suspicion. Clinically, the diagnosis is based on the symptoms of infection: local tenderness over the kidney, particularly over the costovertebral angle; reflex bladder symptoms; abnormalities of the urine; and signs of congestion or other damage to the kidney. The pus and bacteria in the urine and the costovertebral tenderness serve in particular to differentiate infections of the kidney from acute diseases of the abdominal organs, such as the gall-bladder or appendix. The distinction of renal infection from other forms of renal pathology, among them hydronephrosis and tuberculosis, is difficult. In hydronephrosis secondary infection often occurs. Tuberculosis is distinguished by its insidious onset, by the greater frequency of bleeding and of symptoms referable to the bladder, and by the tendency to pyuria in the absence of bacteria demonstrable by ordinary methods. The *tubercle bacillus* can often be demonstrated either by smear or by injection into the guinea-pig. Every patient with renal infection should have the benefit of *x*-ray examination to determine the presence or absence of stone. Practically speaking, there is no essential difference between cystitis and renal infection, since infection of the bladder is nearly always secondary to disturbances higher in the tract. Exact differentiation between various forms of renal disease requires ureteral catheterization and pyelography.

Perinephric abscess may produce effects similar to those of suppuration about the kidney which originates in adjoining organs; indeed, the term has been used to cover suppuration in this region without regard to origin. When, however, the cause lies outside the kidney the term "retroperitoneal abscess" is best employed. The distinction emphasizes the necessity of searching for the cause in organs other than the kidney, but is of little importance in determining the immediate treatment, which is surgical in either case.

Prognosis.—The prognosis of renal infection depends in general on a variety of factors: the severity of the infection, the location of the lesion in relation to drainage, and the degree of renal damage. The severity of the infection is the resultant of two opposing forces, the virulence of the organism and the resistance of the patient; and is shown by the general condition of the subject. The more the lesion is confined to the renal pelvis, and the less it involves the parenchyma, the better the chance of spontaneous drainage and cure, provided always that the urinary tract remains free of obstruction. The degree of renal impairment is demonstrated by clinical observation and functional tests. In acute infections the ultimate damage may be much less than appears at first. The prognosis is largely a matter of the severity of the infection. The mere fact that the disturbance is located in the kidney does not necessarily mean that it will prove harmful in the end. In milder varieties in which the kidney is not damaged the disease appears to be self-limited, as, for example, in the pyelitis of little girls or of pregnant women. In chronic pyelonephritis the course depends upon the extent of the lesions and may be prolonged with remarkably little damage to the renal parenchyma, or when infection is repeated may lead to septicemia or uremia. Perinephric abscesses are unlikely to resolve spon-

taneously, and continue to increase until they rupture into the pleura, intestine, skin, or the true pelvis.

Treatment.—The treatment of infections of the kidney consists in rest, antisepsis, diuresis, changes in the reaction of the urine, and, most important of all, in drainage. Absolute *rest*, flat in bed, is necessary in the acute cases. The kidney requires rest when there is renal impairment, and this may be attained in part by the use of a *nephritic diet*. Uremia requires treatment as in other forms of nephritis. Of urinary antiseptics by far the most efficient is *hexamethylenamine*, which may be given in doses of from 5 to 10 grains, increasing to 20 or 30 grains, three times a day. Since this substance depends for its action on the liberation of formaldehyd, which occurs only in an acid medium, the reaction of the urine should be corrected if necessary. *Diuresis*, by means of water, as a means of washing out the kidney and its pelvis, is very generally employed. The fluid is given by any available route, by mouth, rectum, subcutaneously, or intravenously. In acute cases this treatment should be used with caution because of the congestion of the kidney. Alternate changing of the reaction of the urine is a form of therapeusis which is also widely used. The value of lavage of the renal pelvis through a ureteral catheter is still to be determined. In order to favor drainage in the acute infections by which the patient is confined to bed, the pillow may be removed, and a smaller one inserted posteriorly under the lower chest to expand the lumbar fossæ and imitate the effect of standing. The renal pelvis can often be drained by the ureteral catheter. The use of aspirating needles for the purpose of drainage is now discountenanced, and abscesses beyond the reach of the ureteral catheter are accessible only at operation. Surgery is advisable in pyelonephritis mainly as a remedy for such complications as stone, retention of urine, or acute nephritis. If the disease has reached the stage of pyonephrosis the kidney should be removed. In acute fulminating infections surgical interference is justified only as a desperate measure; but when successful is said to produce striking results. Perinephric abscesses, like any other accumulations of pus, require surgical drainage. Removal of the cause, in particular of retention of urine, infection in the lower urinary tract, or of a focus of infection elsewhere in the body, is obviously important.

HENRY B. RICHARDSON.

HYDRONEPHROSIS

Definition.—Hydronephrosis is dilatation of the renal pelvis, with pressure and atrophy of the renal tissue, as a result of obstruction in the urinary tract.

Etiology.—Blocking of the ureter causes hydronephrosis only when it is gradual, partial, or intermittent; in other words, when the parenchyma is in condition to produce urine under pressure. When the obstruction is sudden and complete, the functional damage is so great that no urine is

secreted, and the result is not hydronephrosis, but anuria. The cause of the obstruction may lie anywhere along the urinary tract. When below the bladder, as it often is in prostatitis and stricture of the urethra, the effects are bilateral; but this type of disturbance is not so much hydronephrosis as infection, since the bladder takes the brunt of the pressure. When it is the ureter which is blocked, the result is essentially hydronephrosis, although secondary infection is common. The cause of the obstruction may lie outside or within the urinary tract, and may be congenital or acquired. Many instances are due to congenital defects: implantation of the ureters at an abnormal angle, at which they are subject to kinking or external pressure; stricture; valves; and aberrant vessels which press on the ureter. Congenital obstruction of the urethra occurs, causing bilateral hydronephrosis. Excessive motility of the kidney, from whatever cause, tends to produce angulation of the ureter and intermittent obstruction. The more common causes of acquired obstruction from within are stone, stricture, foreign body, and tumor. Among the external acquired causes, neoplasm, granuloma, adhesions, operative trauma, uterine displacements, and fecal impaction may be mentioned. Hydronephrosis, like misplacement of the kidney, is more common in women than in men, and on the right side than on the left.

Morbid Anatomy.—As the size of the sac increases, the renal tissue, at first only congested and flattened, becomes thinner, until eventually the kidney is a mere shell surrounding the hydronephrotic fluid. The outer surface of the mass is irregularly ovoid. The fluid is more or less urinous, but is much less rich in solids than the normal urine. A low-grade infection and the formation of calculi are secondary to the other changes. The hydronephrotic kidney varies in size from normal to that of a child's head.

Symptoms.—The outstanding sign of hydronephrosis is palpable enlargement of the kidney, although even this may be lacking. Other symptoms are pain and tenderness, and in some cases oliguria at the time of the pain, with polyuria when it is relieved. When the obstruction is persistent the subjective symptoms are slight, and may be limited to dull pain. The kidney seldom attains a large size, and the urine is normal in amount and character, because the hydronephrotic kidney is blocked, and the other hypertrophied until it can do the work of two. When, however, the obstruction is intermittent, pain and variations in the quantity of urine excreted are marked. During an attack the secretion of the affected kidney ceases, except that the urine accumulates in the sac, causing pain and enlargement of the organ. Hence the association of oliguria with pain and renal tumor. With relief of the obstruction the contents of the sac are suddenly discharged, tension is relieved, and the pain and tumor disappear. At this time there may be hematuria. With movable kidney the attacks may take the severe form known as Dietl's crisis.

The function of the affected kidney is damaged in proportion to the back pressure of the urine; slight impairment may progress to uremia, when the obstruction is bilateral, or when for any reason the unaffected kidney is unequal to the strain put upon it.

Diagnosis.—The intermittent type of hydronephrosis is characterized by the association of pain and renal tumor with oliguria and by their simultaneous disappearance. The tumor is recognized as renal by its position, and at times by the fact that it is traversed by the colon. When large it

may be mistaken in children for *embryoma of the kidney* or *neoplasm* of the retroperitoneal glands, and in women for *ovarian cyst*. The latter is usually more movable, and less effective in filling the lumbar region. *Enlargement of the gall-bladder, cysts of the pancreas or mesentery*, and *encysted ascites* may cause confusion. By means of the cystoscope and ureteral catheter, obstruction, displacement, and dilatation of the renal pelvis, or unilateral impairment of function may be demonstrated.

Prognosis.—The course of the disease is protracted, and spontaneous cure is rare. Death ensues from uremia. The outlook is more serious when the urethra is obstructed, since both sides are affected, and infection is added.

Treatment.—Obviously the sac should be drained, and the cause of the obstruction removed. The only question is as to the method to be used. In the intermittent cases due to movable kidney relief may often be obtained from measures designed to hold the organ in place, such as the wearing of an abdominal corset. Drainage may sometimes be accomplished by the use of the ureteral catheter, but when this is impossible, surgical measures are necessary; the most conservative of these being aspiration of the fluid through a lumbar incision by means of a needle and syringe. Ordinary tapping through the flank is not advisable. Removal of the cause includes a variety of measures, many of them surgical. The earlier the operation and the less the impairment of the hydronephrotic kidney and its fellow, the better the prospect of cure.

HENRY B. RICHARDSON.

NEPHROLITHIASIS

(*Renal Calculus, Stone in the Kidney*)

Definition.—Nephrolithiasis is the presence in the renal pelvis of concretions formed from substances normally in solution in the urine.

COMPOSITION OF STONES.—Renal calculi consist of matter deposited from the urine and gummed together by means of organic substances. Thus Keyes states that ". . . the microscope reveals that a urinary calculus is made up not of sharp-pointed crystals so commonly seen in the urine, but of rounded masses, showing neither angles nor polarity, and consisting of an amorphous collection of granules of a urinary salt embedded in a structureless albuminous substance. . . ." Stones are classified as primary or secondary. *Primary stones* develop in an acid urine without antecedent inflammation; *secondary stones* in the alkaline urine which is the result of infection by the pyogenic cocci or the *Bacillus proteus*. The primary stones are composed, except in very rare instances, of uric acid, calcium oxalate, and the urates of sodium, calcium, or potassium. The secondary stones are commonly formed of mixed phosphates of ammonio-magnesium or calcium, often on a nucleus of primary stone.

Etiology.—The exact reason why solids ordinarily in solution in the urine should be deposited in the form of concretions in certain cases and not

in others is far from clear. Upon certain etiological factors there is, however, fairly general agreement. These are stasis, the participation of colloids in the mechanism, and the necessity for a nucleus around which the calculus may form. It is obvious that if drainage is entirely free the stone will be swept away before it has time to attain any size. Urine is a supersaturated solution, that is, a fluid containing a greater quantity of dissolved substances than could be taken up by a corresponding amount of distilled water, and is, therefore, in unstable equilibrium. The colloids act probably by replacing the normal crystallization by amorphous concretions. They serve also as a nucleus, which may be a blood-clot, the mucopus excited by the irritation of a foreign body, the products of a mild inflammation, or bacteria. Gross infection is, however, more probably a result than a cause of stone. Other factors are of secondary importance. Long-continued restriction of the fluid intake, resulting in an increase in the specific gravity of the urine, may play a part in the etiology of some cases. Variations in climate, diet, mode of life, and in the composition of the drinking-water have been blamed, because of the greater prevalence of the disease in some localities than in others. The presence of crystals in the urine has been regarded as a contributing factor, though these may often be present without stones. Renal calculus is more common in men than in women in the ratio of 100 to 60. It is most frequently seen during the third and fourth decades of life. There is a hereditary factor in some cases.

Three types of stone may be distinguished: The first is the multiple, fine, gritty form, known as "sand." The intermediate sizes are ovoid in shape, and usually single. The largest form of calculus grows until it makes a mold of the entire renal pelvis. The shape of the stone is thus determined by its size and by the shape of the cavity in which it lies. Usually nephrolithiasis is limited to a single stone at a time; or if multiple, it is confined to one kidney. Multiple stones are faceted. With rare exceptions those over 1 cm. in diameter do not reach the ureter.

Symptoms.—The symptoms of nephrolithiasis are pain, albuminuria, hematuria, pyuria, disturbances of urination, and enlargement of the kidney. In the typical form known as *renal colic* the pain is the most severe known, and may resist large doses of morphin. It begins suddenly, often in a person otherwise in the best of health, with agonizing pain referred to the region of the kidney, radiating at first across the abdomen, and ultimately down the course of the ureter to the bladder, symphysis pubis, genitalia, or the inner side of the thigh. It is often accompanied by retraction of the testicle. The radiation corresponds roughly to the progress of the stone down the ureter. The pain is accompanied by faintness, nausea, vomiting, cold sweat, and shock. Often there is incessant stimulus to urinate. The urine is scant, high colored, and frequently bloody.

Such a typical attack is neither constant nor pathognomonic of renal calculus, and, in fact, occurs in only about half of the cases. The manifestations are related to the size of the stone. The smaller the stone, the greater the likelihood of pain; conversely, the large coral-like calculi, which form a mold of the entire pelvis, are likely to be "silent," that is, to cause no symptoms. These are not uncommonly detected by an *x*-ray examination performed for other purposes. In other cases the pain consists of a dull ache, caused by distention of the renal pelvis. The character of symptoms is also related to the position of the stone. If it lodges in the ureter, pain is

practically inevitable. The radiation varies likewise with the location; a stone in the pelvis of the kidney tends to produce a pain which radiates across the abdomen; and stone in the ureter, a pain which travels down the course of this structure. An atypical radiation, observed in rare instances, extends up instead of down. Many patients feel no pain at all. During a typical attack the urine is either suppressed or scant, high colored, and bloody. Abnormalities of the urine occur at one time or another in the majority of cases; of these, albuminuria is the most constant, though its significance is reduced by its prevalence in other conditions. Hematuria and pyuria each occur in slightly less than half of the cases. The former varies not only in occurrence but in intensity between the extremes of a few red blood-corpuscles recognizable under the microscope, and the appearance of gross blood. Furthermore, one and the same patient may have hematuria at one time and not at another, and may fail to pass blood in the urine even immediately after an acute attack.

The painful and frequent urination of renal colic is of reflex origin and may even be excited by a stone which has not left the renal pelvis. It is observed in about one-fourth of the cases.

Palpable enlargement of the kidney is found with about the same frequency, namely, in less than 1 case out of 4. It is presumably due to hydronephrosis or pyonephrosis.

Complications.—The complications of nephrolithiasis are obstruction, infection, and ulceration. Obstruction of the partial or intermittent type causes hydronephrosis, and is associated with a series of attacks of renal colic. When complete the obstruction causes anuria of the affected kidney. Bilateral or complete anuria ensues when both kidneys are blocked simultaneously, when there is but one ureter, when the better of two kidneys is blocked and the other overburdened, and when the opposite kidney is inhibited though normal. Instances of the last condition can be proved but rarely; apparently it is only an unsound kidney that can be inhibited by disease of the opposite side. In contrast to that of nephritis, the anuria of stone is striking because of the mildness of its early symptoms. The patient may apparently continue to enjoy the best of health for four or five days in spite of voiding daily only a few cubic centimeters of urine tinged with blood, or sometimes at rare intervals 2 or 3 liters at a time. Other early symptoms are those of impending uremia; hiccup and vomiting, followed in a day or two by outspoken uremic symptoms, consisting of tense pulse, glazed tongue, constipation, at first partial and then complete, vomiting, depressed mentality, or at times mental excitement, and eventually coma. There is less than one chance in four of spontaneous recovery.

Ulceration may take place at any part of the urinary tract where the stone rests, and is more liable to occur the larger and the less movable the stone. The ulcer may be so deep and extensive as to cause perforation and extravasation of urine, a serious complication. Ureteral stricture may be the result of an impacted stone.

Renal calculus, which is one of the most common causes of infection of the kidney, produces pyelonephritis in the broad sense. When it is chiefly the pelvis which is affected, the disease tends to resemble pyelitis and there is little involvement of the parenchyma or depression of the renal function; but the parenchyma may be affected, and renal insufficiency

result. Usually the disease progresses slowly to the stage of pyonephrosis, or a perinephric abscess develops.

Diagnosis.—Nephrolithiasis is to be differentiated first, from diseases outside the kidney, and second, from other forms of renal pathology. When pain is an outstanding symptom, calculus may be confused with disease of other abdominal organs, of the spine, and of the central nervous system. The data obtained from the history and physical examination tend to rule out these possibilities; and the urinary findings, including the results of microscopical and bacteriological examination, as well as of the functional tests, give evidence of renal disease. If the examination is to be of value the urine must be fresh, and if the patient is a woman must be obtained by catheterization. It is to be noted that small numbers of red corpuscles are present in the urine in a number of conditions unassociated with diseases of the kidney, for example, during appendicitis, either from general toxemia or direct extension of the inflammation to the ureter. Of course, when a stone has previously passed through the ureter, as evidenced by the history or by its presence in the bladder, nephrolithiasis is highly probable. Typical renal colic, though highly suggestive of stone, may occur likewise in Dietl's crisis, or may be excited by the passage of solid matter other than calculi, that is, of crystals or clotted blood. The presence of great numbers of crystals in the urine is of some value, the more so if they are in rounded forms and composed of uric acid or oxalate, or accompanied with red blood-corpuscles. When anuria is the only symptom it may be due to stone, hysteria, or poisoning with bichlorid of mercury.

When the pain is relatively mild, nephrolithiasis needs to be differentiated from tuberculosis and other infections of the kidney, from hydronephrosis, and from neoplasm, since pain and hematuria are common to all these conditions in greater or less degree. The *x*-ray picture does not provide conclusive evidence, since both false positives and false negatives occur; that is to say, the shadow which suggests stone may be due to a concretion outside of the urinary tract, such as a phlebolith; or certain stones may be obscured by bones or otherwise rendered invisible. Confirmation may be obtained by the use of the ureteral catheter, either by means of the waxed bougie, which receives a scratch when it comes in contact with a stone, or by pyelography, *i. e.*, *x*-ray examination of the renal pelvis after it has been injected with some opaque material. The elimination of phenolphthalein through the ureteral catheter gives evidence of the functional capacity of the individual kidney, and therefore provides a means of accurate diagnosis. The frequency with which the usual clinical methods fail to lead to a correct diagnosis, together with the necessity of the data as a guide for treatment, make these special examinations essential.

Prognosis.—Since the damage caused by a stone depends not upon its mere presence in the upper urinary tract, but upon its secondary effects, that is to say, upon obstruction, infection, anuria, renal insufficiency, and ulceration, the outcome of nephrolithiasis cannot be predicted in any given case. Certain facts should, however, be kept in mind. The size of the stone has a bearing on the prognosis; small ones retained by gravity in the lower calyx may do no harm, and others may be expected to pass spontaneously if less than about 1 cm. in diameter. Notable exceptions occur, and much larger stones have been passed spontaneously. Calculi too large or numerous to pass cause obstruction and infection, with their at-

tendant damage to the kidney. The conditions responsible for the formation of calculus continue after its removal, and lead in many cases to new concretions.

Treatment.—The treatment may be classed as preventive, palliative, or operative. The one *method of preventing recurrence* which has received general support is the drinking of ample quantities of water in order to reduce the specific gravity of the urine. Other methods aim to reduce the supply of the substance from which the previous calculus was formed. When this has been shown by analysis to consist of uric acid or oxalate, the corresponding foods may be eliminated from the diet. Since this type of stone develops in an acid medium, the taking of alkali appears rational, and is widely advocated.

Palliative treatment consists in the relief of pain, for which large doses of *morphin*, and even *chloroform*, may be required. *Heat*, in the form of a hot bath, or of local applications, is comforting. If the stone is too large to be passed, as shown by *x*-ray examination, or by prolonged recurrence of colic, it should be removed. In some cases this may be accomplished by manipulation with the ureteral catheter, but more often *operation* is required. Pain which persists for several days is evidence of impaction of a stone in the ureter and blocking of the kidney, a condition which must be corrected. Fever is evidence of infection, and therefore an additional reason for surgery. Anuria demands immediate relief if the patient is to be saved. Surgery should be considered also in the intervals between attacks. Calculi greater than 1 cm. in diameter are unlikely to pass spontaneously, and if retained, sooner or later destroy the kidney. So also do the large coral-like "silent" calculi; but the absence of symptoms shows that infection has not yet occurred and that renal damage is likely to progress less rapidly. Here the possibility of the formation of a similar stone on the opposite side has to be borne in mind. Calculi of all sorts are likely to recur.

Henry B. Richardson.

TUMORS OF THE KIDNEY

Neoplasms of the kidney are rare. They may be benign or malignant and primary or metastatic. When primary they usually originate in the kidney itself and only with extreme rarity in the renal pelvis or ureter. The *benign tumors* which reach a size of clinical importance compose a small minority, and include adenoma, fibroma, lipoma, angioma, and teratoma. The *malignant forms* develop most commonly during two widely separated periods of life—from birth to five years, and from forty-five to sixty-five years of age. Corresponding to these age groups are two main types of tumors, the embryomata of children, and the hypernephromata of adults. According to Grawitz the hypernephromata arise from remnants of embryonic adrenal tissue included within the substance of the kidney. The malignant tumors which are next in frequency in the adult are carcinoma, sarcoma, embryoma,

and adenoma. Primary tumors are unilateral, without predilection for either side. They are seen slightly more often in males than in females.

Symptoms.—The cardinal symptoms and signs of *neoplasm* of the kidney are hematuria, pain, and palpable enlargement of the kidney. Any one may appear without the others. Of the three, *hematuria* is most common as a first symptom, being noticed at the outset in half of the cases, and at some time or other in two instances out of three. At first it attracts attention either because of the discoloration of the urine or the formation of blood-clots. It comes in attacks which become more frequent and more severe with the progress of the disease. Hematuria is usually abundant, painless, and unaffected by rest or exertion. Slightly less common as an initial symptom is the *pain*, which varies in character from a constant dull ache or dragging sensation to outspoken colic; the former due to the distention of the pelvis or capsule, the latter to the passage of blood-clots. Radiation to the genitalia or back occurs. When the tumor presses on a nerve the pain is neuralgic in character. *Palpable enlargement* of the kidney is much less common as an early sign, and at the outset occurs in only 20 per cent. or less of the cases. The tumor grows progressively, and unless checked by operation or death can be felt sooner or later. Its shape depends on the manner of growth of the neoplasm; infiltration produces enlargement without distortion, but encapsulation forms a lump. The tumor descends on inspiration if the growth has not extended to the surrounding tissue. *Anemia* and *cachexia* are late manifestations. The *renal function* is little changed; in the absence of hematuria the urine may be quite normal, and even on the diseased side the function may remain unaffected. An unusual symptom, but common enough to arouse suspicion of renal tumor, is *varicocele*, which is attributed to pressure on the spermatic vein, and, unlike the usual type, does not subside when the patient lies down.

Diagnosis.—Confusion arises not so much when hematuria and tumor co-exist, as when one is present without the other. The differential diagnosis varies according to which is present. Thus, the bleeding associated with a neoplasm may be confused with *"essential" hematuria* in spite of the fact that it is unilateral. This limitation to one side is also a means of differentiation from the *hematuria of nephritis*, and diagnosis is confirmed by the absence of other evidences of the latter disease. In *tuberculosis of the kidney* the bleeding is less severe, occurs at an earlier age, is more often accompanied by pyuria, and is usually associated with a characteristic cystoscopic picture. Furthermore, the injection of the urine into a guinea-pig produces the changes typical of tuberculosis. The hemorrhage of nephrolithiasis is less severe and less spontaneous. Should the stone escape detection by *x*-ray examination, it can often be demonstrated by the ureteral catheter. When the enlargement of the kidney is the only symptom, it can sometimes be distinguished from tumors of the abdominal or pelvic organs or of the retroperitoneal tissue by its position, shape, and the fact that the colon passes over it. Of local conditions in the kidney those most likely to be confused are *hydronephrosis* and the closed type of *pyonephrosis*. Special methods of examination may be necessary for differentiation. *Congenital cystic kidneys* are functionally impaired, include both sides, as may often be demonstrated by physical examination, and cause changes which produce a peculiar shadow during pyelography. With neoplasm the outline

of the tumor may appear under the x-ray in thin individuals. Pyelography demonstrates a recognizable deformity of the renal pelvis in more than a majority of the cases.

Prognosis and Treatment.—Malignant disease of the kidney progresses more or less rapidly to cachexia and death. The treatment is nephrectomy, unless definite evidences of metastasis are already present. The immediate mortality is 10 to 20 per cent., or even more. Recurrences are almost universal; only one person in five survives the third year after operation, and only one in ten the fifth.

HENRY B. RICHARDSON.

CYSTIC DISEASE OF THE KIDNEY

By far the most common type of cysts of the kidney is that sometimes known as *cystic degeneration* or *congenital polycystic kidneys*. This disease is encountered in infants, but is exceptionally rare in childhood, and appears most often between the fortieth and sixtieth years of life. It is somewhat more common in the female than in the male. The condition is usually bilateral, but one kidney is ordinarily much more affected than the other.

Etiology.—The mechanical defect upon which the disease depends is occlusion of the urinary tubules. The continued secretion of urine under pressure causes the formation of multiple cysts, which grow at the expense of the renal tissue and cause enlargement of the kidneys as a whole—often to several times the normal size. As to the fundamental cause of the occlusion many theories have been advanced; the disturbance has been attributed to inflammation and new growths of one sort or another. The weight of opinion favors neither of these, but rather the theory of a congenital malformation. The secreting and the collecting portions of the kidney develop from two different layers of the Wolffian system, and subsequently unite to form a channel of communication. Failure of the normal union causes obstruction and the formation of cysts.

Morbid Anatomy.—The degree of enlargement of the kidney depends on the number and size of the cysts scattered through it. Commonly the organ is two or three times the normal size, at times a great deal larger. It tends to retain its normal shape. The numerous cysts which project from the surface give it a rough and knobby appearance. On section others are found scattered irregularly through the substance. The parenchyma is more or less thinned, according to the degree of pressure, and may be so scant as to be invisible to the naked eye. The contents of the cysts may be urinous or serous; sometimes bloody. The cysts do not communicate with the pelvis or the calyces. Their presence is frequently associated with malformations elsewhere in the genito-urinary tract, or with cysts in other organs, especially the liver.

Symptoms.—The most important symptoms are pain, enlargement of the kidney, and the signs of chronic nephritis. The first to be noticed is

the *progressive enlargement of the kidney*, which may antedate the other manifestations by a period varying from a few months to a number of years. The *pain*, which is due to the enlargement, is felt in the region of the kidney, is dragging in character, and is often increased by exertion or relieved by lying down. At first it is paroxysmal, later continuous. When hematuria is present the passage of a clot of blood may cause renal colic. Contrary to the accepted belief, the tumor is *palpable on one side only* in the majority of cases. The percussion note may also be increased in extent. The enlargement tends to push the colon forward or to the inner side; in the former case the resonance may be detected over the tumor mass. In thin subjects the irregular surface of the projecting cysts may be palpated.

The *nephritis* produced by the pressure of the cysts is of the chronic type associated usually with hypertension and arteriosclerosis. The specific gravity of the urine is decreased and the amount increased, especially the night specimen. The specific gravity becomes relatively fixed. Albumen and casts appear in the urine, and in some cases blood. The disease progresses until death is caused by uremia or circulatory complications.

The large polycystic kidney tends to slip down, and in doing so may cause *hydronephrosis* by angulation of the ureter. Sometimes it becomes infected.

Diagnosis.—Bilateral tumor of the kidney, associated with nephritis and pain, offers little diagnostic difficulty, but the great majority of cases are so atypical that relatively few are recognized. The symptoms of nephritis may predominate, and the tumor escape recognition. When unilateral the mass suggests *malignant disease*, but the absence of cachexia and the presence of nephritis should point to cystic degeneration. *Hydronephrosis* tends to be intermittent instead of progressive, particularly the type which produces a large kidney. *Pyonephrosis* usually causes pus to appear in the urine. *Simple cysts* do not cause nephritis, and *hydatid cysts* are associated with the presence of hooklets in the urine from time to time. Catheterization of the ureter is a useful means of ruling out some of the other local conditions; and pyelography demonstrates a broadening of the calyces, with displacement of the renal pelvis as a whole. Such data are of positive diagnostic value in about half of the cases.

Prognosis.—In the newborn the disease is rapidly fatal, and in infants only slightly less so. In adults it may be latent for several years, and then progress rapidly to uremia or cerebral hemorrhage and death; or the active symptoms may persist for several years.

Treatment.—The *nephritis* should be treated as if due to other causes. *Rovsing's operation* has been performed several times, with apparent benefit. It consists in puncture or aspiration of the larger cysts, and is capable of relieving the parenchyma from pressure and reducing the kidney to a third of its former abnormal size. Patients have been reported to live as long as five years after this operation. In the rare instances in which only one kidney is involved, and the other remains normal as to size and function, *nephrectomy* may be considered.

Other Forms of Cysts.—*Multiple retention cysts* are found at autopsy in patients with chronic nephritis, but are of no clinical importance. A rare condition, observed in adults usually after the age of forty, is the *simple* or *solitary cyst*, which develops in the kidney, as a rule in the cortex, and projects outward as it grows. When it enlarges it causes a dull dragging

sensation or ache in the loin or hypochondrium which is aggravated by exertion. When palpable the tumor feels firm and elastic. The growth is benign. Treatment consists in operative drainage of the cysts, with destruction of the secreting membrane.

Echinococcus cysts constitute a stage in the life-cycle of the *Tenia echinococcus*, which is found as a tapeworm in the intestine of carnivora, particularly the dog, and infects man by way of the stomach and intestines. Passing to the tissues by way of the blood-stream, this organism lodges in the kidney in 5 per cent. or less of the cases of infection, the low incidence being due probably to the complicated path it has to pursue to reach this organ. Once the embryo has entered the kidney it grows with the formation of scolices and daughter-cysts. The age at which renal infection is most common is from twenty to forty years. The disease is unilateral. The *symptoms* are those of a slow-growing tumor, namely, dragging pain and enlargement in the loin. There is little to distinguish the cyst from any other tumor until it ruptures, usually into the renal pelvis. The passage of the contents of the cyst down the ureter provokes the symptoms of colic, and often hematuria, and for a time the hooklets may be found in the urine. Much more rarely the cyst ruptures into the gut or peritoneum; in the former case it becomes infected and pyonephrosis results; in the latter, peritonitis develops which is usually of a low grade, but may sometimes be fatal. It is complicated by urticaria or even by anaphylactic symptoms excited by the liberation of the contents of the cyst into the peritoneal cavity. The general features of echinococcus infection, that is, the eosinophilia and the complement-fixation reaction, are helpful in diagnosis, and the finding of hooklets in the urine is, of course, conclusive. The severity of the infection varies; the disease may be relatively harmless or fatal. In some instances the growth is extremely slow. Spontaneous cure takes place in a minority of the cases in which the cyst ruptures into the renal pelvis. The treatment consists in removal of the cyst, which, as a rule, implies removal of the infected kidney as well.

Henry B. Richardson.

DISEASES OF THE BLOOD-FORMING ORGANS

ANEMIA

Definition.—The term "anemia" is applied to any deficiency in the quantity or quality of the blood as manifested by a reduction in the number of red corpuscles or in the amount of hemoglobin, or in both.

Etiology.—In the past, anemia has been divided into two groups—primary and secondary—a classification based on the fact that the etiology of certain blood-deficiency diseases was unknown. These were, therefore, called primary anemias, but further study indicates that discovery of their exact cause only requires time. Although this classification of anemia is still in common usage, it is evident that all anemia is secondary to one of the following three causes: (1) loss of blood; (2) increased destruction of blood; (3) defective formation of blood.

To these Lee and Minot add another, *i. e.*, a deficient delivery of erythrocytes to the circulation from bone-marrow which is apparently functioning normally. Any factor which causes a diminution of blood over a long period of time may induce activity of another; for instance, continual hemorrhage or persistent destruction of blood accompanied by hyperfunction of the bone-marrow may eventually so fatigue the hematopoietic tissue that the production of blood becomes deficient.

Local Anemia.—Although anemia usually involves the entire body, a part of the body, or even a single organ, may be made anemic when some local or general circulatory change reduces the local supply of blood. Consideration of such a condition belongs more properly to the chapter dealing with diseases of the cardiovascular system, but it should be pointed out here that the results of such circulatory defects are similar to those of general anemia as far as the organ involved is concerned. Thus, a vasomotor constriction, like that of Raynaud's disease, causes coldness and numbness of the fingers; a dilatation of the splanchnic vessels may produce anemia of the brain and unconsciousness; and a sclerosis of the arteries may result in degeneration of an organ. All these changes cause, among other things, local anoxemia. Since general anemia also reduces the oxygen supply, anoxemia develops whether the anemia is due to a cardiovascular lesion or to blood deficiency.

ACUTE ANEMIA

Etiology.—The most common cause of acute anemia is hemorrhage, but certain intoxications like acute lead or benzol poisoning, and overwhelming infections, such as pernicious malaria, acute endocarditis, or septicemia may cause severe anemia in a very short time. As a rule, however, acute anemia is associated with sudden and rather profound loss of blood. Acute loss of blood takes place in traumatic severance of blood-vessels, rupture of viscera, lesions of the gastro-intestinal tract, particularly gastric or duodenal ulcers, typhoid fever, and erosions of gastric arterioles or varicosities, hemorrhagic pancreatitis, ectopic gestation, placenta prævia, pulmonary tuberculosis, and after operations.

Morbid Physiology.—Probably the best description of this condition has been published by Lee and Minot. The seriousness of an acute hemorrhage depends entirely upon the amount of blood lost and the rapidity of bleeding. Thus, if one-third of all the blood is lost suddenly, death follows unless the blood is immediately replaced, although an individual may be deprived of two-thirds of his blood within twenty-four hours, and still recover. As a general rule, if the quantity of hemoglobin is reduced to less than 25 per cent. of normal, life is impossible.

The immediate result of an acute hemorrhage is a *polymorphonuclear leukocytosis* which usually develops within a few hours. The number of *blood-platelets* increases during the first day after hemorrhage and reaches maximum in a few days. At first the red cell count and percentage of hemoglobin remains normal because the blood volume is decreased. This, however, soon changes, because dilution of the blood by fluid drawn from the tissues makes manifest the diminution in the number of erythrocytes and in the quantity of hemoglobin. Following severe hemorrhage the greatest dilution occurs after two or three weeks; the blood does not return to normal for several months. Within the first forty-eight hours after the hemorrhage young cells appear in the circulation as the result of stimulation of the bone-marrow. These are chiefly reticulated cells and are often present in as great a concentration as 10 per cent. Occasionally normoblasts are seen. The fact that the red cells are replaced more rapidly than the hemoglobin accounts for the low color index and achromia. Complete recovery from severe hemorrhage may take several months.

Symptoms and Signs.—The symptoms and signs of marked hemorrhage are very striking and develop rapidly. The patient feels weak and faint, becomes dizzy and quite thirsty, and may vomit. The *pulse* is rapid and weak; the *skin* dusky, pale, and cold; the *temperature* subnormal, and the *respiration* weak and shallow. The individual is *restless* and, if hemorrhage continues, delirium frequently ensues. Finally, a cold perspiration breaks out and the patient rapidly passes into a state of shock and coma. During this condition the change in *blood-pressure* is characteristic. At first the diminution of the blood volume causes a reflex constriction of the arterioles which prevents any marked change in blood-pressure and may even cause a slight rise. With continued loss of blood the pressure declines gradually, until at systole it is between 75 and 90 mm. of Hg. This is called the *critical pressure*. If bleeding continues, the pressure drops suddenly and markedly and shock supervenes. All the symptoms and signs of acute loss of blood are due to anoxemia and depend upon a diminution of the blood volume.

Diagnosis.—The history and often the continuation of hemorrhage, the appearance of prostration and air-hunger, the weak rapid pulse and falling blood-pressure, and the characteristic blood-picture of a leukocytosis, decreased blood volume, and appearance of young red cells are all evidence of the loss of blood.

Prognosis.—The outcome of the condition depends entirely upon the amount and rapidity of blood loss, the promptness with which treatment is started, and the ease with which the hemorrhage may be stopped. Thus, ruptured gastric varices or an exsanguinating hemoptysis is stopped with difficulty, while bleeding from an external wound is in most cases readily controlled.

Treatment.—The entire treatment of acute loss of blood consists in measures for stopping the hemorrhage and for increasing immediately the blood volume. Blood-pressure readings should be taken every half hour, and if the critical level (75–90 mm. Hg at systole) is approached, emergency treatment should be instituted at once. Transfusion from a compatible donor is probably the most efficacious form of treatment. Temporarily saline may be injected intravenously or, better still, 300 to 500 c.c. of 10 per cent. glucose solution intravenously followed by a hypodermoclysis of 1000 c.c. of saline. Cannon suggests the use of a mixture of saline and gum acacia to increase the blood volume. Usually 500 c.c is the maximum amount used. If the hemorrhage is not from the gastro-intestinal tract, fluids may be given by mouth. The patient should be kept quiet. If necessary morphin may be given. Warmth is essential, but care must be taken to avoid still further loss of fluid by perspiration. If the blood volume can be maintained above critical limits and the hemorrhage stopped the majority of patients recover.

CHRONIC ANEMIA

Chronic anemia may be due to a variety of causes, the more common of which are:

(1) *Hemorrhage.*—The most frequent conditions which cause long-continued bleeding are hemorrhoids, gastric or duodenal ulcer, uterine lesions, and cirrhosis of the liver. The bone-marrow in such cases undergoes a compensatory hyperplasia. The appearance of the blood and the signs and symptoms resemble those of acute anemia except that they are less marked and are characterized by more gradual changes.

(2) *Defective Blood Formation.*—The formation of blood may be defective because of: (*a*) a defect in the delivery of blood-cells to the circulation; (*b*) intoxications; (*c*) exhaustion of bone-marrow; and (*d*) atrophy of bone-marrow.

The first group includes the condition which Lee and Minot consider not really a diminution in the production of blood, but essentially a defect in the delivery of cells to the blood by the bone-marrow. The condition of the blood is like that observed during a distinct failure to produce blood and is characterized by a low reticulated count. The bone-marrow is hyperplastic. The true nature of this anemia is not understood.

Aplastic anemia may be caused by certain intoxicating agents, chief among which are benzol, radium, *x*-ray, trinitrotoluol, and arsphenamin. Occasionally it is associated with severe sepsis; and recently nephritis has been shown to play an etiological rôle. Probably the best known examples of the exhaustive type of this anemia are seen in the terminal stage of pernicious anemia and in some cases in which the loss or destruction of blood is continued. The bone-marrow shows aplasia of red marrow with fatty and fibrous replacement. Small areas of compensatory hyperplasia occasionally occur. The blood is deficient in red cells and hemoglobin, but no achromia is present. Lymphocytes predominate, although leukopenia is invariable and thrombopenia marked. A prolonged bleeding time and poor clot retraction are characteristic. Aplastic anemia is frequently seen in young people and may run a very rapid course.

Myelophthisic or atrophic aplastic anemia is produced by tumors which crowd out the hemopoietic tissue. Multiple myeloma, metastatic carci-

noma, hypernephroma, and leukemia may produce such a condition. This is characterized by an initial irritation of the bone-marrow with an increase in the number of polymorphonuclear leukocytes, platelets, and young red cells, followed by a distinct aplasia.

(3) *Blood Destruction.*—Destruction of blood is perhaps the most common cause of the chronic anemia which may vary from a mild, almost low normal condition, to that of a rather severe grade. Increased destruction is evidenced by an increased quantity of pigment in the serum, bile, stools, and urine; an increase in the number of fragmented red blood-cells; and an increase in the activity of the bone-marrow which is made apparent by the presence of many young forms in the blood.

The more common causes of destruction of blood are:

(*a*) *Chemical Poisons.*—Coal-tar derivatives and lead compounds are frequently associated with anemia because of their wide-spread use. The anemia of lead poisoning has been shown by recent investigations to be due probably to the action of lead on the surface of the erythrocytes. The cells become more fragile and are less able to withstand the trauma of circulation.

(*b*) *Infections.*—Anemia of some degree is usually associated with typhoid fever, acute rheumatic fever, subacute bacterial endocarditis, sepsis, scarlet fever, malaria, and certain stages of syphilis. Any long-continued and draining illness, such as tuberculosis, abscess of the lung, empyema, or osteomyelitis, causes some destruction of blood. Parasitic infections, especially *uncinariasis* and *bothriocephalus latus,* are frequently accompanied by marked anemia.

(*c*) *General Toxemia.*—Examples of general toxemia are the distinct hemolytic anemias of chronic nephritis and of jaundice.

(*d*) *Pregnancy and Puerperium.*—Anemia is often associated with pregnancy and the puerperium, but is frequently of so mild a grade as to be overlooked. Puerperal anemia must be considered the result of destruction of blood since it is characterized by an increase of pigment in the serum and urine. The presence of many young cells in the blood indicates active regeneration.

(*e*) *Hemolytic jaundice* is usually considered a primary disease of the spleen, and will, therefore, be discussed with the diseases of the spleen. It is of interest, however, to point out here that the patient suffers from a chronic anemia characterized by marked destruction of blood. The spleen, liver, and kidneys become tinged with blood-pigment; there is a marked hyperplasia of the bone-marrow, and the number of microcytes and of reticulated cells in the blood is increased. These young erythrocytes may come to constitute 25 to 30 per cent. of the total number of red cells. Bile is usually absent in the urine except during exacerbations, but urobilin is present. One of the characteristic features of this condition is the marked decrease in the resistance of the red blood-cells to hypotonic saline solution. Normal erythrocytes begin to hemolyze in a saline solution of about 0.45 per cent. and are completely laked by concentrations of 0.35 to 0.3 per cent. In hemolytic jaundice hemolysis may begin in 0.7 per cent. and be complete in solutions of 0.5 to 0.45 per cent.

Miscellaneous Anemias.—Certain types of chronic anemia depend on several factors for their production, while the etiology of others is, as yet, unknown. These may be conveniently referred to as miscellaneous anemias.

Chlorosis is a disease which is of interest largely because of its history. It was rather common in the latter half of the nineteenth century, but in recent years has almost entirely disappeared. Girls, usually of the working class and more especially Irish immigrants of the blond type, were most susceptible. Improper nutrition, poor hygiene, hard work, constipation, and menstrual disturbances were considered important factors in its etiology. The striking feature of this disease is a marked reduction in the hemoglobin percentage, with a relatively slight diminution in the number of red cells. There is no evidence of an increased production of young cells, but the platelet count is raised. The patient shows a greenish pallor of the skin; weakness, but usually no loss of weight; and usually breathlessness, palpitation, and some edema. Thrombosis of the femoral veins or occasionally of the cerebral sinuses is not uncommon.

Neoplasms.—The cause of the anemia associated with malignant tumors is not known, although several factors doubtless play a part in its production; hemorrhage from the neoplasm, for example, possibly inanition, and most probably a toxin elaborated by the necrosing tumor which affects the production of blood and may cause some destruction. Ash has shown that simple starvation causes little change in the blood. It is, therefore, probable that an impaired ability to absorb food and malnutrition cannot entirely explain the condition. Further contributing causes are secondary infection of the neoplasm with hemolytic organisms, and invasion of the bone-marrow by metastases which may interfere with the formation of young erythrocytes.

Anemia of Childhood.—Anemia commonly occurs in various conditions during childhood. Insufficient intake of iron is not infrequently the cause of one type of nutritional disturbance. Anemia associated with enlargement of the spleen constitutes another large group of blood-deficiency diseases in children. This group will be considered in the chapter dealing with Diseases of the Spleen.

Sickle-cell anemia has recently been described by Huck, Sydensticker, and others. It occurs in negroes, is probably familial, and is characterized by a reduction in the number of erythrocytes in the blood and by the appearance of sickle-shaped red cells. Patients suffering from this disease have a red cell count of approximately 2,500,000, a color-index slightly below 1, a moderate leukocytosis, and a distinct eosinophilia. Nucleated red cells and some diffuse and punctate basophilia are commonly present in the blood. Often the characteristic sickle-shaped cells do not appear until after the blood has been allowed to stand.

Pernicious Anemia.—As far as we know now pernicious anemia is primarily caused by destruction of blood. At certain stages of the disease, however, faulty production becomes an important factor. Because of its rather distinct characteristics it is usually considered a definite clinical entity, and will, therefore, be discussed in detail as a separate disease of the blood.

Symptoms and Signs of Chronic Anemia.—These depend on the condition from which the anemia results. In general, the patient feels weak, tires easily, becomes dyspneic on exertion, and may complain of faintness, vertigo, and palpitation. Pallor, rapid pulse, and slight dependent edema are often present. As the changes in the blood depend on the etiology and severity of the anemia, no single description can fit the great number of

variations. Usually the percentage of hemoglobin shows more reduction than the number of red blood-cells, so that the color index is less than one.

Treatment of Chronic Anemia.—The success of the treatment of chronic anemia depends entirely upon whether or not the cause may be removed. Anemia due to hemorrhage can be cured by preventing the loss of blood. If necessary, surgical intervention should be undertaken. Bleeding fibroid tumors of the uterus may be treated with radium. Frequently a supportive transfusion may be necessary before the patient can undergo an operation. Once the cause of the hemorrhage is removed, recovery is usually assured. The patient should have the benefit of abundant fresh air, sunlight, and a nourishing diet, which should contain spinach, meat, and liver. Ordinarily administration of iron is not necessary if the food is ample in quality and quantity.

The defective formation of blood due to leukemia or tumor invasion can only be treated symptomatically. When the condition is due to toxins, such as benzol, or when it is caused by sepsis, these factors must be eliminated and supportive transfusions of blood employed. Iron may be given in the form of Blaud's pills, the cacodylate of iron, or the green citrate.

The cause of blood destruction must be removed. This is relatively easy when the diminution of blood is due to some exogenous poison. In infections, the treatment depends entirely upon the eradication of the infecting organism. The anemia of pregnancy and of the puerperium can be treated only by supportive measures, since the direct etiology of the disturbance is unknown. Transfusions are usually given and ordinary hygienic measures should be employed. Splenectomy is the almost specific therapy for hemolytic jaundice.

Chlorosis is successfully treated by instituting good hygienic conditions, by correction of constipation, and by ingestion of iron, usually in the form of Blaud's pills. Iron is also specific for the iron starvation of children.

Recently Leake and Evans have used desiccated bone-marrow and spleen in the treatment of chronic anemia, with good results. Such therapy is contra-indicated in pernicious anemia, however, because it decreases the blood-count.

In general, the treatment of chronic anemia consists in removing the cause first and then assisting the hemogenic function of the body, which, under normal circumstances, is capable of maintaining an adequate supply of blood. When such a procedure is impossible, therapeutic measures must be considered only palliative.

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PERNICIOUS ANEMIA

Definition.—Pernicious anemia is a grave progressive disease interrupted by remissions "occurring without any discoverable cause whatever." It is characterized by certain changes in the blood and blood-forming organs, in the central nervous system, and in the gastro-intestinal tract.

History.—In 1855 Addison published an article, "On the Constitutional and Local Effects of Disease of the Suprarenal Capsules," in which he included a lucid description of the clinical manifestations of pernicious anemia and recognized this disorder as a clinical entity. Nearly twenty years later Biermer again described the condition, drew attention to the changes in the blood, and proposed the name "pernicious anemia," by which the disorder is now generally designated.

Etiology.—The cause of the disease remains unknown. It is a disorder of middle life; a few cases begin in the third decade. It does not occur in childhood, and is rare in individuals more than sixty years of age. In a compilation of 371 cases from various sources 209 were males and 162 females. Little is known concerning its geographical distribution except that it is wide-spread in the white race, particularly among people of Nordic origin. It has been observed in mulatto negroes. The evidence of *familial occurrence* is meagre. It is said that there is a high incidence of *achylia gastrica*, possibly congenital, among healthy members of families in which pernicious anemia has occurred; and this disturbance is known to have preceded the development of anemia by many years. Although achylia is the most constant feature of the disease, and persists through all remissions, it is probably no more than a predisposing cause, since all patients with achylia do not have pernicious anemia. Toxic or infectious agents have been thought to gain access to the gastro-intestinal tract because of the absence of hydrochloric acid in the stomach. Recently attention has been called by Moench, Kahn, and Torrey to the fact that in pernicious anemia the number of *Bacilli welchii* in the feces is greater than in any other condition. Hunter has attached great significance to an infection causing the *glossitis* which is frequently, but not invariably, associated with this disease. The pathogenesis is most obscure. Some of the hosts of the tapeworm *Dibothriocephalus latus* develop an anemia which is practically indistinguishable from pernicious anemia. Similar blood changes have been noted in *uncinariasis*. *Extracts from the larvæ of certain parasitic flies* and injection of *toxins*, such as ricin, produce an experimental anemia in which the changes in the blood more or less closely simulate those of pernicious anemia. Occasionally in *gastric carcinoma* the blood changes may resemble those of pernicious anemia. Current opinion differs as to whether the disease is primarily a destruction of blood with abnormal hematopoiesis, or whether this process plays a minor rôle which is secondary to an abnormality of blood formation and pigment metabolism.

Morbid Anatomy.—The body is well nourished and the skin is lemon colored. A moderate amount of yellow-stained fat is present; the muscles are darker red than is normal. The amount of blood in the body is diminished. The heart is flabby and its muscle undergoes exquisite fatty change which is well seen under the endocardium of the left ventricle where there are yellowish streaks of fat in the muscle, the so-called "tigering." The lungs may have a brownish tint due to the deposition of granules of an iron-containing pigment.

Examination of the gastro-intestinal tract shows in most cases that the tongue is smooth and red, and that the papillæ have disappeared at least on the margins. There is sometimes marked atrophy of the gastric mucosa. These changes are not invariable. The liver is enlarged and may be seen under the microscope to contain fat; in the cells are granules of hemosiderin, an iron-containing pigment. These granules of hemosiderin are found in other organs, such as the lungs, spleen, pancreas, and kidney. The spleen is often enlarged, but its cut surface is not abnormal. The kidneys are pale and somewhat browner than usual because of the presence of hemosiderin granules in the convoluted tubules. The bone-marrow undergoes important changes: the medullary cavity is occupied by a red, gelatinous marrow which replaces the fat, a condition best seen in the long bones, such as the femur. This red marrow is composed of erythroblastic areas, and, as well as the spleen and liver, contains large cells which engulf red blood-corpuscles. In many cases examination of the spinal cord discloses foci of degeneration which are particularly marked in the posterior and lateral tracts of the cervical portion of the cord. Microscopically it may be seen that these are purely degenerative in character, and that glial reaction is absent. Here too phagocytic cells may be seen. More recently attention has been called to the presence of similar foci of degeneration in the brain. Peripheral nerve lesions have been described, scattered degenerations being shown in both Marchi and Weigert preparations.

Morbid Physiology.—The total quantity of blood is decreased, chiefly by reduction of the number of red cells. Both Bock and Denny have estimated by different methods that the volume of plasma is nearly normal. Campbell finds that the average size of red blood-corpuscles in pernicious anemia may be as much as 30 per cent. above normal, but the concentration within them is normal. The corpuscle has a high color index and a high volume index. The ability to transport oxygen is, of course, directly proportional to the hemoglobin content of whole blood. The capacity for transportation of carbon dioxid has been found by Barr and Peters to be reduced; in spite of a considerable alkaline reserve, the CO_2 absorption curves of blood in pernicious anemia were found to be rather flat, so that large differences in CO_2 tension produced relatively little change in the CO_2 content of the blood. One might assume that compensation for this reduction in both oxygen and carbon dioxid carrying capacities would be affected by an increased rate of circulation of the blood. Some observations of Fahr and Ronzone tend to support this supposition, as do the animal experiments of Morawitz and Deneke. The increased demand upon the heart muscle, with its own limited oxygen supply, may result in sufficient dilatation to account for the so-called "hemic murmurs" so often heard during severe anemia. The edema may also be related to the fact that the myocardial reserve is being encroached upon even during rest. Dyspnea at rest is not common, but breathlessness quickly develops on exertion, partly, no doubt, as the result of the diminished cardiac reserve and partly because of the diminished ability of the blood to exchange gases.

The digestive functions may be considerably impaired. Soreness of the tongue may render mastication imperfect. The gastric achylia makes gastric digestion impossible, and there is usually a rapid emptying of the stomach. Attacks of diarrhea are frequent, but usually respond promptly to the administration of hydrochloric acid with the food.

The renal function is often impaired, although anatomical evidence of nephritis is rare (Christian). This functional disturbance usually occurs when the anemia is marked and disappears when it improves. The specific gravity of the urine becomes lower and tends to be fixed. The index of excretion of urea may be quite low, and the phenolsulphonephthalein excretion is also usually low. E. S. Stieglitz has pointed out that iron has antidiuretic properties, and that the functional disturbance may be due to deposition of excess iron in the kidneys. Complete anuria or marked renal insufficiency is rare except in the severe reactions following transfusion which are probably due to incorrect matching of the bloods of donor and recipient.

There is great confusion about pigment metabolism. The facts are that the blood-plasma in pernicious anemia frequently contains increased amounts of pigment and bilirubin, and occasionally small amounts of free hemoglobin. Jaundice also may develop, with fever and enlargement of the liver and spleen. At such times the number of red blood-cells decreases rapidly and there is an increased excretion of urobilin. Both these phenomena are generally considered evidence of blood destruction, which is thought to result chiefly from the activity of the reticulo-endothelial system in the spleen, hemolymph-nodes, bone-marrow and liver (Peabody and Broun), or from fragmentation (Rous). Whipple does not believe that destruction of blood plays an important rôle in the pigment metabolism of pernicious anemia. He has brought evidence to show that there is an increased formation of a substance which he calls "pigment complex" and a decreased formation of stroma. Pigment complex may be formed from food or body protein, including hemoglobin, and may give rise to hemoglobin, bile-pigments, and possibly to urochrome and urobilin. Reformation of hemoglobin from bile-pigments is denied, as is also the absorption of stercobilin in the intestine.

Ashby has found little evidence that destruction of blood is an important factor in pernicious anemia. Most clinical observers readily concede that this may be a secondary matter in pernicious anemia, but it is generally conceded that the rapidly falling counts are due to a destruction of blood.

Symptoms and Signs.—Pernicious anemia produces a well-defined syndrome. It is a disorder which, to quote Addison's able description, "makes its approach in so low and insidious a manner that the patient can hardly fix a date to the earliest feeling of that languor which is shortly to become so extreme." This *languor* or *weakness* is usually the first symptom of which the patient complains, and even if not present at the onset it appears sooner or later during the course of the disease and dominates the picture. Simultaneously with the weakness a *yellowish pallor* is usually noticed and *gastro-intestinal disturbances*—anorexia, vomiting, and particularly diarrhea—become evident. Two other symptoms, occasionally initial, must be mentioned: the recurrent "*sore tongue*," which Hunter has emphasized, and the *sensory change* in the extremities, often described as a feeling of numbness or tingling. Either or both of these may usher in the disorder; and their occurrence should, therefore, always suggest the possibility of incipient pernicious anemia. As the disease progresses the weakness becomes more pronounced and the lemon-yellow pallor still more evident. Soon other symptoms appear which are seen in every variety of anemia—palpita-

tion, shortness of breath, headache, and slight edema of the legs. A common and important feature is the *remissions*, during which the patient somewhat rapidly regains his strength; these will later be discussed more fully.

On examination, the first point to attract the observer's attention is the lemon-yellow color of the face and the pallor of the lips. This lemon tint is somewhat characteristic and at once suggests the diagnosis. In some cases only a simple pallor is seen, and, more rarely, obvious jaundice. *Petechiæ* may occasionally appear in the skin over the body. There is usually some loss of weight, but the *nutrition* remains good. *Fever* is commonly present, especially during the periods of active destruction of blood, the temperature ranging between 99° and 101° F. The *scleræ*, usually bluish white, may be icteric when there is marked blood destruction. Retinal hemorrhages are occasionally seen. Examination of the mouth may, in addition to pallor of the mucous membrane, reveal a *tongue* which is smooth, red, and glazed, with atrophic papillæ and superficial excoriations at the edge. This change, however, is neither constant nor peculiar to pernicious anemia. The tongue is nearly always uncoated. *Pyorrhea alveolaris* is very common. The *pulsation of the arteries*, particularly in the neck, is marked. The *heart* beats rapidly, but is not enlarged. A soft systolic murmur which is most marked at the base is usually heard over the precordium. The *liver* is rarely markedly enlarged. The *spleen* is palpable in about half the cases. Gross enlargement of these viscera is uncommon. Of special importance from many points of view is the *absence of gastric secretion* which is demonstrated by the test-meal. The constancy of achylia gastrica is important for diagnosis.

The *urine* occasionally contains traces of albumin, and at times hyaline casts. Urobilinuria is practically constant. Functional tests show that the renal activity is impaired when anemia is severe, although usually there is no anatomical evidence of nephritis.

Abnormalities in the *nervous system* are manifested in about 80 per cent. of the cases by paresthesias and disturbances of the objective senses, such as loss of the sense of position and vibration, and occasionally by some superficial hypesthesia. In some patients an increase of the reflexes of the lower limbs is associated with the sensory loss or occurs alone. These changes may progress until the clinical aspect is that of subacute combined degeneration (posterolateral sclerosis). An interesting type of case is that in which the *cord symptoms* are primary and predominant; in these patients other symptoms, and even the change in the blood-picture, may not appear until the subacute degeneration is advanced. Psychoses are occasionally encountered; the patient is generally irritable and often somewhat querulous and difficult to handle.

The Blood.—The changes in the blood in pernicious anemia vary considerably according to the stage of the disease. Usually there is a diminution in the number of red cells, white cells, and platelets. The *red cell count* may be as low as 3,000,000 even in remissions, and during the active stage may fall to 500,000. In no other condition is the oligocythemia so marked. The *volume* of the blood is considerably reduced. As a rule there is *leukopenia* except during remissions, when the count may be normal or high because of increased bone-marrow activity. The number of platelets is usually diminished except during remissions. The *percentage of hemoglobin* is usually higher than the number of red cells would warrant, al-

though in certain stages of the disease, especially remissions, the color index may be one or less. This, however, is not common. The *volume index* is always greater than one. This is the volume per cent. (hematocrit) divided by the red cell count in percentage of 5,000,000.

There is considerable evidence of *increased destruction of blood* even during remissions. The quantity of *serum pigment* is always increased and microcytes and other fragmented cells are usually present. As a rule there is no change in the *bleeding time* and only a negligible retardation of *coagulation time*. On examination of the stained smear during exacerbations the leukopenia and diminution in the number of platelets are quite apparent. There is marked anisocytosis with predominance of macrocytes, marked poikilocytosis, and diffuse and punctate polychromatophilia. A variety of nucleated red cells may be seen, some containing hemoglobin with small pyknotic nuclei, others larger and paler, with irregular or fragmented nuclei. The typical megaloblast is quite large (over 11 micra in diameter), and pale, with a large oval nucleus containing a fine network of chromatin. Mitoses are occasionally seen. Special stains for the reticulum of red cells reveal an increased percentage of reticulated cells during the early stages of remissions, and very low percentages in the aplastic stages.

When the bone-marrow becomes exhausted and there is insufficient regeneration the anemia reaches a stage which is considered by some to be a distinct type of disease—*aplastic* anemia. Sometimes this condition occurs with the very first symptom and runs a rapid and fatal course. It is characterized by a marked oligocythemia, leukopenia, thrombopenia, and tendency to purpura. The fact that there is no evidence of active bone-marrow function in the smear is especially important.

Prognosis and Course.—Before the advent of liver therapy the outlook was grave. Recovery was very rare. The process was occasionally arrested for several years, but the great majority of patients died within three years.

The downhill course was interrupted, in fully 80 per cent. of the cases, by periods of apparent recovery, which lasted, as a rule, for three or four months, occasionally for four or five years. The usual number of remissions was two, but four or five were sometimes seen when the course of the disorder was prolonged. The patient, during these remissions, often showed complete subjective recovery, but the apparent improvement was not accompanied by corresponding changes in the blood-picture, which still preserved its abnormal features, although not quite so clearly. It was interesting to notice how well a patient appeared to be during a remission even when there was relatively little change in either the number or morphology of the red cells.

In the smaller group of patients who had no remissions the course of the disease tended to be rapid, and death usually ensued within six to nine months.

Diagnosis.—Any case of severe anemia for which no cause can be discovered should be suspected of being pernicious in nature. Although study of the blood usually contributes considerable information about the condition, a diagnosis based upon examination of the blood alone is unjustifiable. In pernicious anemia, achylia gastrica is always present. When even small amounts of hydrochloric acid are present in the gastric contents the diagnosis is questionable. Neurological disturbances and the history or presence of glossitis are valuable confirmatory evidence.

The anemia due to the *broad tapeworm* (*Bothriocephalus latus*) closely

resembles pernicious anemia, but may be differentiated by an examination of the stools. In the later stages of *sprue* anemia is often associated with glossitis and achylia gastrica. In this disorder, however, the gastro-intestinal symptoms are very marked and extreme emaciation occurs. Occasionally *carcinoma of the stomach* may be associated with changes in the blood resembling those of pernicious anemia; the differential diagnosis depends upon the discovery of the gastric tumor, and the presence of occult blood in the stools or vomitus. Secondary anemias, aplastic anemia, chronic bacterial endocarditis, hemolytic jaundice, and Addison's disease also at times bear a superficial resemblance to pernicious anemia. The severe but unexplained anemia, the characteristic blood-picture, the achylia gastrica, glossitis, and evidence of changes in the spinal cord are all important points of evidence which point to a diagnosis of pernicious anemia.

Treatment.—The dramatic success of the liver diet in pernicious anemia has changed the entire outlook of this disease. Minot and Murphy have reported brilliant results in applying to pernicious anemia Whipple's and Robscheit-Robbins' demonstrations that liver, and to a less extent apricots, peaches, and certain leafy vegetables, induce rapid blood regeneration in dogs rendered anemic by bleeding. These results have been widely confirmed, revolutionizing the treatment of the disease.

Minot prescribes daily from 120 to 240 gms. of liver, occasionally substituting kidneys; 120 gms. or more of muscle meat; not less than 300 gms. of vegetables, especially spinach and lettuce, under 10 per cent. carbohydrate; 250 to 500 gms. of fruit, peaches, apricots, etc.; fat kept as low as possible (40 gms.); dry bread, potatoes, and cereals to bring calories up to 2000 to 3000; sweet foods omitted and free sugar used sparingly.

Very ill patients may refuse food at first. When persuasion fails, raw liver juice may be given by tube. A simple hydrochloric acid extract (0.1 per cent. HCl) of ground liver (boiled one minute and filtered, then concentrated until 50 c.c. equals 250 gms. of raw liver) has served to initiate remissions in our clinic, after which it was possible to give a diet similar to Minot's in the majority of instances.

A liver extract is now in the process of preparation which will simplify the therapy very much.

During exacerbations *rest in bed* is essential. The administration of *dilute hydrochloric acid*, which may be sipped throughout each meal, should be continued during the whole course of the disease. Diarrhea is readily controlled by this procedure. For the glossitis the important treatment is the *correction of all dental defects*, careful cleansing of the teeth after meals, and the use of a potassium chlorate mouth-wash. The eradication of all possible *foci of infection* is desirable.

In the past *transfusions of blood* were widely used with little evidence of permanent benefit. *Arsenic*, *iron*, and *splenectomy* have not been successful.

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A. G. Maitland-Jones.

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THE LEUKEMIAS

Definition.—Leukemia may be defined as a pathological condition in which there is extensive hyperplasia of the leukoblastic tissues, with the appearance in the peripheral blood of abnormal white cells. Two forms of leukemia may be distinguished by the type of cell which undergoes proliferation. This cell may originate either in the bone-marrow (myeloid leukemia) or in the lymphoid tissue (lymphoid leukemia).

The outstanding clinical features of fully developed classical leukemia are: (1) a pronounced quantitative *increase* and qualitative change in the leukocytes of the blood, and (2) varying degrees of splenic and glandular enlargement. Leukemia differs from extreme degrees of leukocytosis in that the peripheral blood contains immature white cells which have probably entered the circulation from the bone-marrow, lymph-glands, or other hemopoietic tissues before complete development. It is this qualitative and not the quantitative change which permits clinical differentiation of leukemia.

Increased knowledge has forced us, however, to extend the bounds of this classic definition and, in the absence of a known etiology, to base a new definition on the pathology. Patients are sometimes seen whose blood-picture during life is characteristic of leukemia, and yet at autopsy there is no evidence of leukemia. This is probably merely an instance of abnormal response of the bone-marrow to various stimuli, such as infections, toxins, etc. On the other hand, the blood-picture may have been subleukemic or even normal during life, although autopsy reveals leukemic changes in the tissues (aleukemic leukemia). Leukemia must, therefore, be considered as a disease characterized by several states, rather than as a clinical entity. In all of these states, however, there is histological evidence of leukemic hyperplasia, although the clinical manifestations may vary greatly from those usually associated with leukemia—marked leukocytosis and enlargement of the spleen and lymph-nodes.

History.—In 1845 Hughes Bennett and Virchow independently described the peculiar white appearance of the blood at autopsy, the massive enlargement of the spleen, and the presence of exceedingly large numbers of leukocytes in the blood. Bennett called the disease *"leucocythemia";* Virchow, *"leukemia."* Both failed to observe that the white blood-cells differed qualitatively from those found during sepsis. Virchow later distinguished a "lymphatic" and a "splenic" form of the disease, while in 1870 Neumann, after noting changes in the bone-marrow, proposed the term "myelogenous" to describe the third type. Ehrlich, however, who introduced the differential staining of leukocytes in 1891, distinguished two types of cells in leukemia: (*a*) granulocytes, granular leukocytes of bone-marrow origin, which occur in splenomyelogenous or myelogenous leukemia, and (*b*) non-granular cells of lymphatic origin seen in lymphatic leukemia. This division is still that most satisfactory and generally accepted.

Incidence.—Leukemia is widely distributed in the animal kingdom. It frequently occurs in fowls, and has been described in horses, cattle, dogs, rats, and mice.

In human beings it is relatively infrequent, 1 case occurring among every 1000 hospital admissions. It occurs at any age, but the various types each seem to develop at a definite time of life. In analyzing 729 cases Ward found that chronic myelogenous leukemia developed most often in patients between twenty-five and forty-five years of age; chronic lymphatic leukemia, in those between forty-five and sixty years; and acute leukemia, in individuals less than twenty-five years old.

Males are more subject to this disease than females. A familial character has been ascribed to leukemia, but there is no valid evidence that heredity is a factor. Leukemia may occur during pregnancy, but no relationship between the two conditions has been proved.

Etiology.—The cause of leukemia is unknown. Various micro-organisms and microbodies have been seen in leukemic blood and tissues, but there is no convincing proof of their etiological relationship. The lesions of leukemia bear a striking resemblance to certain infections and also to a group of tumors. The disease may closely resemble certain types of Hodgkins' disease, and is probably identical with chloroma.

Types of Leukemia.—Leukemia is here discussed under the following headings:

1. Chronic myeloid leukemia.
2. Chronic lymphatic leukemia.
3. Acute leukemia:
   (*a*) Acute myeloblastic leukemia.
   (*b*) Acute lymphatic leukemia.
4. Unusual forms of leukemia and related conditions:
   (*a*) Aleukemic leukemia.
   (*b*) Chloroma.
   (*c*) Leukemic blood-picture due to malignant disease of marrow.
   (*d*) Leukemic blood-picture due to infection.
   (*e*) Leukanemia.
   (*f*) Mixed-cell leukemia.
   (*g*) Pseudoleukemia.

Chronic Myeloid Leukemia.—Etiology.—The cause of chronic myeloid leukemia is entirely unknown. Males are attacked about twice as frequently as females. The disturbance may occur at any age, but is more common between twenty-five and forty years of age and is rare before twenty years of age. There are no recognized predisposing factors.

Morbid Anatomy.—The *postmortem* findings characteristic of the disease are confined chiefly to the blood and the blood-forming organs. The *total blood* volume is usually increased, and the occurrence in the heart and veins of large clots of a peculiar greenish-white color is often noted. The great increase in the number of leukocytes gives to the coagula the appearance of pus. The enormous enlargement of the *spleen* is characteristic. This organ may weigh from 2 to 10 kilograms, but retains its normal shape and notches. The capsule is thickened, and the enlargement is caused by proliferation of the fibrous tissue which is resistant to cutting. On section the surface varies in color from reddish brown to uniform gray, according to the amount of fibrous tissue present. The malpighian bodies are not visible. Infarcts and areas of hemorrhage may occur.

In the early stages the splenic enlargement may not be pronounced, but later it may be so great that the spleen extends below the pelvic brim and to the right of the navel; indeed, not infrequently, it may fill practically the entire abdomen. The normal shape of the organ is, however, preserved. It is of firm consistency and has a sharp medial edge with one or two characteristic notches.

The normal bright yellow "*fat marrow*" in the shafts of the long bones is, as a rule, replaced by a firm homogeneous, pale, yellowish-gray or even pinkish-gray tissue. Traces of normal marrow may remain, or in excep-

tional cases the marrow may have a greenish hue resembling that of the deposits seen in chloroma. In striking contrast to chronic lymphatic leukemia, this type of the disease is not generally associated with gross enlargement of the lymphatic glands.

Marked symmetrical enlargement of the *liver* is characteristic; the weight varies from 2 to 6 kgm.

Macroscopic changes in the heart, lungs, kidney, adrenal, thyroid, ovary, central nervous system, and other organs are extremely rare. Histologically the degree of myeloid change varies in different organs and in different cases. The changes consist in filling of the capillaries with myeloid cells and in occasional small linear collections of these cells parallel to and outside of the blood-vessels. Groups of myeloid cells which may resemble tumor-like nodules may at times be found in the tissues.

Morbid Physiology.—The *nitrogenous balance* is usually negative in acute and variable in chronic leukemia. The endogenous uric acid excretion and the uric acid content of the blood are generally increased. There is often a retention of *phosphates*. *x*-Ray and radium therapy increase remarkably the excretion of nitrogen, uric acid, and phosphates.

In both chronic lymphatic and myeloid leukemia there is a marked *rise in the basal metabolism* expressed in terms of body surface area. The average increase over the normal is between 45 and 50 per cent. The cause of the increase is uncertain; some believe it is due to the active metabolism of large numbers of immature white cells which require an increased quantity of oxygen.

In myeloid leukemia, experimental phagocytosis in the blood becomes less active as the cells depart from the adult type. Although the relative number of adult cells may be less, the absolute number is markedly increased.

That bacterial antibodies, such as agglutinins, are formed slowly, if at all, by leukemic patients, may perhaps explain the fact that in the course of this disease mild infections often prove so severe.

Packard and Ottenberg believe that there is a *leukotoxic factor* in lymphatic leukemia. In a patient with chronic lymphatic leukemia who received transfusion, all the granular leukocytes of the donor's blood disappeared from the circulation within twenty-four hours.

The blood, during both acute and chronic myeloid leukemia, has been shown to contain a *proteolytic ferment*, which cannot be found in lymphatic leukemia.

Oxidizing ferments are present in the polymorphonuclear leukocytes, myelocytes, and generally in the myeloblasts. They have never been demonstrated in lymphocytes. The oxydase or peroxydase is detected by means of special stains (Graham or Goodpasture's) which may be applied both to blood-smears and tissue sections.

Symptoms.—The *onset* is gradual and insidious as a rule. The patient usually complains first of symptoms due to the greatly enlarged spleen, such as a sense of weight or dragging, or of those which result from anemia, such as languor, pallor, weakness, loss of weight, vertigo, palpitation, dyspnea, or intestinal disturbances. Hemorrhage from the nose, bowel, or elsewhere is common in the later stages of the disease, and contrasts sharply with that of acute leukemia which is from the gums, mouth, and into the skin, and is an early and prominent symptom. Slight irregular fever is

not unusual. High temperatures of 102° to 104° F. may be encountered in the terminal stages or in the acute exacerbations of chronic cases, but are more frequent in the acute leukemias. Chills followed by profuse sweating occur during the course of the disease. Leukemic patients tolerate low temperature well, probably because of the increase in their basal metabolism.

The *splenic enlargement* is the most characteristic clinical feature of the disease, and may cause marked symptoms of pressure. Besides the dragging sensation of weight or a sense of fulness there may be pain or sensitiveness to pressure, the result of infarction and perisplenitis.

Such peritoneal irritation may cause a palpable or audible friction-rub over the spleen, and lead to spasm of the abdominal muscles. The spleen may suddenly increase in size as a result of internal hemorrhage; or become smaller under the influence of arsenic, *x*-ray, radium, or benzol, or as the result of an intercurrent infection.

The *liver* is enlarged and its smooth firm edge may be felt sometimes as low down as the umbilicus. The size of the *lymph-glands*, on the contrary, is increased slightly, if at all. *Bone-marrow* lesions produce no constant local clinical symptoms or signs. Bone pains and sensitiveness to percussion of the sternum are very inconstant, but might possibly be attributed to changes in the marrow or periosteum in some cases.

Changes in other organs also deserve mention. *Retinal lesions* are very frequent. The fundus may turn a uniform brownish color from which arteries and veins are not clearly differentiated, and there may be white flecks or streaks with a red border, and hemorrhages similar to those of pernicious anemia. The vision is rarely impaired. *Deafness* with tinnitus and vertigo (Ménière's syndrome) may occur in the late stages when the labyrinth is involved. Organic changes in the *lungs* are rare. Cough and dyspnea with basal edema are not infrequent, and may be attributed to weakness of the myocardium and the mechanical interference caused by abdominal distention and splenic enlargement. *Ascites* has been frequently observed. It is partly due to local congestion and partly to leukemic infiltration of the omentum and peritoneum. The ascitic fluid is clear, but may contain many cells, a large number of which, as in the pleural exudate of leukemia, may be myelocytes. In a large majority of cases the *urine* contains albumin and casts. This is not necessarily, however, a sign of nephritis. The large quantities of uric acid found in the urine result from the destruction of leukocytes. Gout is, nevertheless, almost unknown among leukemic patients. In the female, irregularities of *menstruation* are not infrequent. In the male, *priapism* occurs, though not as often as is generally supposed, as a result of myelocytic thrombosis or infiltration of the corpora cavernosa. Symptoms due to leukemic changes in the *brain* and *spinal cord* are comparatively rare. Cerebral hemorrhage, causing hemiplegia and cranial nerve palsies, is occasionally observed. Leukemic involvement of the *skin* is rare in myelogenous leukemia, but more frequent in chronic lymphatic leukemia. Purpura and petechial hemorrhages are common, especially in the late stages of the disease.

The *blood-picture* is by all means the most characteristic and interesting diagnostic feature of chronic myeloid leukemia. In the early stages the gross appearance is normal, but very soon the color becomes pale as the quantity of *hemoglobin* is reduced, often to 40 or 60 per cent. or less. The *red blood-cell* count falls with this diminution in the quantity of hemoglobin,

so that counts of 2,000,000 to 3,000,000 cells per cubic millimeter are often obtained when the patient is first seen. The color index is generally low. Slight *anisocytosis* with rather noticeable *poikilocytosis* is the rule. In severe cases *megalocytes*, such as are seen in pernicious anemia, are found. *Polychromatophilia* and *basophilic stippling* are consistently observed. The *red cells* are often nucleated; normoblasts predominate, but megaloblasts can be found in some cases. The number of *blood-platelets* is increased. The *white blood-cell* count is frequently several hundred thousand and may even rise above 1,000,000 per cubic millimeter. Such counts may be reduced to normal or subnormal by an intercurrent infection, or, particularly, by *x*-ray and radium therapy. It is not so much the total number of white blood-cells, but the presence of myelocytes and myeloblasts in the peripheral blood which is of significance.

In a stained blood film from a patient with typical leukemia there is: (1) a great relative and absolute increase in the number of ordinary polymorphonuclear neutrophilic leukocytes (they comprise 30 to 80 per cent. of all the white cells); (2) a relative and absolute increase in the eosinophilic and basophilic leukocyte count as a rule; and (3) cells may be found which normally occur only in the bone-marrow, (*a*) myelocytes with neutrophilic, eosinophilic, and basophilic granulations (the percentage of the neutrophilic type is usually the highest and may be 40 per cent. or more), (*b*) myeloblasts (1 to 3 per cent.). Such cells appear in very much larger numbers during the acute exacerbations of chronic myelogenous leukemia and in the definitely acute cases. Large mononuclear and transitional cells are not numerous as a rule, and when many myeloblasts are present may be difficult to identify surely. The percentage of lymphocytes is greatly reduced, but the absolute number increased. Care must be taken to avoid confusion with small myeloblasts.

Of the frequent variations from the above picture, the most striking is perhaps the change in the percentage of myeloblasts. These cells increase in number remarkably at times in chronic cases just before death, and after a remission of the disease which has been induced by *x*-ray, radium, or benzol therapy, or intercurrent infection. This is probably the result of extreme stimulation of the bone-marrow, which causes emission of the very youngest and most immature type of myeloid cells into the circulating blood. In certain cases when from the onset the percentage of these cells is large and there are relatively few myelocytes in the blood, myeloblasts may be readily mistaken for lymphocytes (for differentiation see Acute Myelogenous Leukemia).

Diagnosis.—The diagnosis is generally suggested by the symptoms: first, by those due to the great enlargement of the spleen, such as a sense of weight or dragging; and second, by those which are the result of anemia, such as languor, pallor, weakness, loss of weight, vertigo, palpitation, dyspnea, or intestinal disturbances. The characteristic blood changes above described confirm the diagnosis.

Prognosis.—The disease in the chronic form progresses usually until death occurs on the average in about three years, although patients may live for even ten years. The spontaneous remissions so common in pernicious anemia rarely if ever occur, although very complete temporary remissions may be induced by therapy or intercurrent infection. Death results from the general exhaustion of severe anemia, from hemorrhage, or

from secondary infection. When fatal in less than six months the disease is usually of the acute myeloblastic type.

Treatment.—The treatment of leukemia was largely empirical or symptomatic, until it was found that certain agents more or less specifically reduced the number of white blood-cells. Fowler's solution, cacodylate of soda, and more recently arsphenamin are used to combat the associated anemia. The injection of blood, the administration of iron in various forms, and of red bone-marrow have also been advocated. Metals in the colloidal state are said to have caused improvement. Remission of the chronic type of the disease is common after benzol, *x*-ray, and radio-active substances, notably radium. The acute form of leukemia is apparently not influenced by any treatment.

Benzol is best administered in capsules (preferably coated with salol) containing 0.5 gm. mixed with equal parts of olive oil to diminish its irritating local action. The initial daily dose of two such capsules should be increased to ten. They should be taken immediately after meals; and it is preferable that patients be carefully watched in the hospital throughout such treatment. It is customary to stop administration when the white count has been reduced to 20,000. The administration of benzol is not without danger because of the marked leukopenia with increasing anemia which it may excite, and because it may produce certain toxic effects, such as gastro-intestinal disturbances, headaches, dizziness, skin eruptions, bronchial and renal irritation, and hemorrhages, which may follow its administration. If, however, benzol is given carefully it is of definite value in a considerable percentage of chronic cases.

The *Roentgen ray*, if applied over the enlarged glands or spleen, with the proper technic of "deep therapy" and "cross-fire" usually causes remarkable remissions in the chronic disease. Caution should be taken to avoid injury to the overlying skin and the so-called toxic constitutional effects.

Radio-active substances, notably *radium*, probably provide the best means of treatment now at our disposal for chronic leukemia, particularly of the myelogenous type. Surface application of radium over the enlarged spleen produces striking improvement; the blood-picture becomes almost normal; the spleen and enlarged glands are reduced to almost normal; and the emaciated and weak patient may become plump and strong. The duration of such remissions varies from months to years. Radium treatment is not regarded as curative; yet this is believed to be the safest as well as the most prompt palliative of chronic leukemia. It is probable that the actual duration of life is not in the average case prolonged by any form of treatment; but radiation, in the majority of cases of chronic myelogenous leukemia, increases the duration of efficient life at least 30 per cent.

Chronic Lymphatic Leukemia.—Etiology.—The cause of chronic lymphatic leukemia is unknown. Males are affected twice as frequently as females. The disease develops most frequently late in life, as a rule in individuals between forty-five and sixty years of age. There are no known predisposing factors.

Morbid Anatomy.—The general enlargement of the *lymphatic glands* is usually readily visible to the naked eye. The glands lie singly or in chains, and are only exceptionally matted together. Their size varies from that of a bean to that of a small hen's egg. The cut surface is smooth, homogeneous, soft, grayish-white or reddish-gray in color, and shows an occasional small

hemorrhage. The *thymus* is usually enlarged. The size of the *spleen* is rarely as great as in chronic myelogenous leukemia, but this organ regularly undergoes symmetrical enlargement of varying degree. The cut surface varies in color from grayish red to dark red, occasional follicles are visible, and the density is increased only after long-continued proliferation of the fibrous tissue. Infarcts are common. The normal yellow *marrow* of the long bones is replaced by a dense cellular tissue of a grayish-red color which is homogeneous as a rule, but may occasionally contain nodular areas. The *liver* is generally enlarged. The normal markings on cut section are clear because of the infiltration of lymphocytes into the periportal connective tissue. The *kidneys* may show linear markings due to a similar collection of lymphocytes. The *tonsils*, Peyer's patches, and solitary lymph-nodes of the intestine share in the hyperplasia.

Leukemic deposits are occasionally found in the larynx, trachea, skin, nerves, and meninges. Histological evidence of lymphoid infiltration has been recorded in practically every organ and tissue in the body.

Morbid Physiology.—The morbid physiology of chronic lymphatic leukemia was discussed with that of chronic myeloid leukemia.

Symptoms.—The clinical manifestations of chronic lymphatic leukemia so closely resemble those of the chronic myelogenous form that differentiation can be made with certainty only by examination of the blood, although the splenic enlargement is usually less and the glandular involvement more extensive in the lymphatic variety. The disease begins insidiously, and usually only the accidental discovery of several enlarged painless lymph-glands or of an enlarged tonsil first causes the patient to seek medical advice. In other cases increasing weakness, loss of weight, enlargement of the abdomen, or some symptom associated with anemia may be the first abnormality noticed. Hemorrhage occurs more often in the acute than in the chronic type of the disease. Fever of slight or varying degree may develop.

The most constant and important physical finding is the general extensive enlargement of the glands. The cervical, axillary, and inguinal nodes, which are regularly involved, vary in diameter from a few millimeters to several centimeters. *x*-Ray examination often shows enlargement of the mediastinal glands, and rarely the abdominal lymph-glands may be felt. The glands are firm, discrete, and free from primary inflammatory changes.

Cases of lymphatic leukemia without palpable lymph-glands have been reported, but are extremely rare. As a rule the adenopathy is more pronounced than in the myeloid type.

The spleen is enlarged in practically every case, although the average size is smaller than that encountered in the myelogenous forms, but, exceptionally, massive enlargement of the spleen may be found in lymphatic leukemia. The anatomic notches and smooth surface are preserved in such instances.

The liver can generally be felt from one to four finger-breadths below the costal margin. Rarely in advanced cases it may attain much larger size, although the splenic enlargement usually exceeds the hepatic.

The other lymphatic organs, such as the tonsils and follicles of the mucous membrane, like nearly all the organs of the body, share in the lymphoid proliferation to some degree. In only a few, however, do the clinical changes require mention. Although disturbance of vision is rare, typical leukemic

changes may be seen in the *fundus of the eye*. Lesions of the skin are more common in lymphatic than in myelogenous leukemia and are very varied. Pruritus, prurigo, urticaria, bronzing, vesicles, pustules, localized infiltrations, nodules, and tumors have been described.

The presence of albumin and casts in the *urine* is very common, but of no diagnostic significance. The excretion of uric acid is constantly increased, but to a less degree, as a rule, than during myelogenous leukemia. Bence-Jones proteinuria has been reported by several authors.

In the terminal stages the symptoms relative to the heart, lungs, and digestive tract may be similar to those described under Chronic Myelogenous Leukemia.

Blood-picture.—In the early stages the red blood-cell count and hemoglobin content are normal or nearly so, but later both are reduced and the color index becomes low. The white blood-cell count is, as a rule, lower than in myelogenous leukemia, averaging between 100,000 and 200,000 per millimeter. Higher counts are rare.

The stained blood-smear when the disease is well established is very typical. The leukocytes are strikingly uniform, 90 to 99 per cent. being practically identical with the small lymphocytes of normal blood, except for the smaller rim of protoplasm and the great decrease in the number of "azurphile" granules which are normally present in 30 to 40 per cent. of lymphocytes. The extreme fragility of the pathological lymphocytes is shown by the presence of protoplasmic smudges (so-called *Gumprecht shadows*). The count of the other leukocytes of the blood is generally decreased both relatively and absolutely. Abnormal myeloid cells are lacking. The blood gives a negative oxydase test and contains no peptic ferment.

When the disease is advanced, anisocytosis, poikilocytosis, polychromasia, and basophilic stippling of the red cells may be observed, and normoblasts and, more rarely, megaloblasts are present in the blood-smears. The number of blood-platelets is decreased.

Diagnosis.—The diagnosis is suggested by enlargement of the lymph-glands and spleen and by symptoms of anemia. The characteristic blood changes are confirmatory evidence.

Prognosis.—In the majority of cases the disease runs a chronic course. Remissions may occur spontaneously, or as the result of treatment or intercurrent infection. Almost invariably the disease leads to death within from two to ten years.

Treatment.—The treatment of chronic lymphatic leukemia is essentially the same as that of chronic myelogenous leukemia. Radiation, when employed, should be similarly applied over the enlarged glands.

Acute Leukemia.—Definition.—Acute leukemia presents a very characteristic syndrome and is rapidly fatal. It may be divided into two types which are differentiated by the type of cell which predominates in the blood: (*a*) acute myeloblastic leukemia; (*b*) acute lymphatic leukemia. This division is frequently difficult and is of more interest to hematologists than to clinicians. In many instances the cells may be so immature that even histological study of the tissue after death fails definitely to demarcate the myeloblastic from the lymphatic type.

Etiology.—The cause of acute leukemia is unknown. The disease develops more frequently in individuals less than twenty years of age, and affects males twice as often as females. There are no recognized predis-

posing causes or diseases. Blood-cultures often contain streptococci or other organisms, but these are regarded as secondary invaders.

Symptoms.—Not infrequently after some infection, such as tonsillitis, a furuncle, or an abscessed tooth, a patient is taken suddenly ill with high fever, headache, general malaise, and extreme prostration, as if he were suffering from a severe, malignant, infectious disease. Pallor increases rapidly. There is a marked tendency to hemorrhage from the gums, nose, stomach, rectum, or in the fundus of the eye. Swelling and ulceration of the gums, cheek, jaw, and tonsils is frequent and often leads to severe gangrenous lesions in a very short time. Purpuric hemorrhages of the skin are rarely absent. The regional lymph-glands of the neck and jaw enlarge so rapidly that they are frequently operated upon before the true nature of the disease is suspected. The other lymphatic nodes may undergo slight, but rarely marked, enlargement. There is moderate enlargement of the spleen in the majority of cases, but it may easily escape detection. The liver may be palpable. Vomiting and diarrhea may occur. Albumin and casts are present in the urine. The temperature ranges from 102° to 104° F.

Less frequently Ménière's syndrome may appear as the result of involvement of the labyrinth, or palsy of the cranial nerves, pleural effusion, and sensitiveness of the bones to pressure.

Diagnosis is difficult only when the blood is not examined. The stained smear contains a large number of abnormal mononuclear cells. Clinically the condition may be confused with purpura hæmorrhagica, Ludwig's angina, ulcerative stomatitis, infective endocarditis, septicemia, hemorrhagic forms of acute specific fevers, diphtheria, typhoid, typhus, lymph-gland tuberculosis, and acute infectious mononucleosis.

Prognosis.—Acute leukemia is in most cases rapidly fatal; death occurs within a few days or weeks. Remissions are very rare and the possibility of spontaneous recovery doubtful.

Treatment.—The treatment is entirely symptomatic. Arsenic, benzol, *x*-ray and radium therapy are not even of temporary benefit.

(*a*) *Acute myeloblastic leukemia* may occur as a primary disease, or not infrequently in the terminal stages of chronic myelogenous leukemia.

Morbid Anatomy.—The gross changes resemble those of chronic myelogenous leukemia, the spleen, lymph-glands, and bone-marrow being involved. There is a greater tendency to hemorrhage and ulcerative lesions in the mouth, but the spleen and lymph-glands are usually less enlarged. Histological evidence is usually necessary for differentiation of this type of acute leukemia. There is typically a suppression of lymphoid-cell activity, and a diffuse hyperplasia of the myeloid elements in spleen, lymph-glands, liver, and bone-marrow. The myeloblast usually predominates in all the organs. A positive oxydase test or the demonstration of a proteolytic ferment in the tissues is positive evidence of the myeloid nature of the disease. The fact that very young myeloblasts may fail to give these tests may render differentiation from the acute lymphatic disease extremely difficult.

The Blood.—The rapid and progressive decrease in the number of red blood-cells and in the quantity of hemoglobin produces a very severe anemia, so that the blood often contains normoblasts, megaloblasts, and has a high color index, a condition which may resemble that of the blood

during pernicious anemia, especially when there is leukopenia. Red counts of 1,000,000 and a hemoglobin content of 20 per cent. are often seen. The total count of white blood-cells is frequently low at the onset and may remain low throughout the course of the disease, the average figure being about 30,000 per cubic millimeter. In some instances there is a rapid rise from day to day which amounts finally to several hundred thousand. The predominant cell is the myeloblast. At first glance a smear appears to contain large lymphocytes which suggest acute lymphatic leukemia, but careful examination usually shows that many of these lymphoid-like cells contain fine neutrophilic granules, and are actually forms transitional between myeloblasts and myelocytes (premyelocytes). These three types of cells constitute 30 to 60 per cent. or more of the white cells. Mature polynuclear leukocytes are very rare. In some cases in which small myeloblasts are present the resemblance to lymphocytes is even greater. The oxydase test, if positive, gives proof of the myeloid origin of the cells; if it is negative, there is still room for debate, since very young myeloblasts do not react positively.

(*b*) *Acute Lymphatic Leukemia.*—The older view that acute leukemia was nearly always of the lymphatic type has been rejected. More careful cytological study of blood and tissues with the use of the oxydase stain tends to show that acute myeloblastic leukemia is much more frequent than the acute lymphatic type.

Morbid Anatomy.—The gross lesions of this form are only slightly different from those of chronic lymphatic leukemia. The spleen and lymph-glands are, as a rule, less enlarged. There is the same tendency to hemorrhage and to ulcerative lesions of the mouth and throat as in acute myeloblastic leukemia. The predominant infiltrating cell in all the tissues is the lymphocyte, and there is aplasia of myeloid cells in the marrow. This change may be diffuse or restricted to tumor-like nodules suggesting lymphosarcoma. The oxydase test is negative.

Blood.—There is a severe anemia from the onset; the red cell count is 1,000,000 per c.mm. or less, and the hemoglobin percentage below 20. The color index may be high. Normoblasts are usually present and occasional megaloblasts. The number of leukocytes is often below 10,000 when the patient is first seen, and leukopenia may persist throughout the entire course; in other cases after being very low at the onset, the white count gradually rises to a number varying from 20,000 to 100,000 or more; as a rule, however, it remains lower than in the chronic form of the disease. Lymphocytes are predominant (90 to 99 per cent.) and either the small or the large variety may be more numerous. The number of polynuclear neutrophilic and eosinophilic leukocytes is greatly reduced both relatively and absolutely. A few myelocytes may be produced by stimulation of the bone-marrow.

Unusual Forms of Leukemia and Related Conditions.—Many conditions occur in which the changes in the leukopoietic tissue and the blood approach or resemble those of the types of leukemia already described, but differ in some particulars. Very little is known about these conditions.

(1) Aleukemic leukemia is the term used to designate the leukemia during which the total white blood count remains normal, although there are qualitative changes in the blood and leukemic changes in the tissues.

(2) Chloroma was formerly classed with the tumors, but is now believed

to be closely related to, if not actually a form of, leukemia. Its characteristics are remarkably similar to those of the acute types of leukemia, and in many instances the clinical symptoms, blood-picture, course, and pathological changes are identical with those of acute leukemia. The green color of the nodules on section, and the peculiar tendency for subperiosteal proliferation to cause symptoms of pressure about the orbit, were at one time considered infallible differential points, but have since been found inconstant and, therefore, unreliable. The two types of chloroma—(*a*) myelogenous chloroma of Naegeli (chlor-myelo-sarkomatosis of Sternberg) and (*b*) lymphatic chloroma (chlorolymphosarkomatosis of Paltauf; chloroleukosarkomatosis of Sternberg)—are differentiated by the type of hyperplastic cell encountered. The former type is by far the more frequent.

(3) Response of Bone-marrow to Malignant Disease.—The bone-marrow may as a result of malignant disease throw immature marrow cells into the circulation. The appearance of myelocytes alone, even up to 20 per cent., is not to be considered as proof of leukemia. *Postmortem* examination may fail to show diffuse myeloid infiltration of the leukoblastic tissues.

(4) Response of Bone-marrow to Infections.—In certain infections cells of the myelocytic series are not infrequently present in the peripheral blood. These are to be regarded as the results of bone-marrow stimulation. Slight areas of myeloid proliferation may be found in some organs after death, but such lesions must be wide-spread before they can be considered leukemic.

(5) Leukanemia.—The term *leukanemia* should be discarded. It was used by von Leube to describe a case which had the features of pernicious anemia and of leukemia, and which was probably severe infectious anemia, with myelopoiesis. Careful study of such cases usually shows them to be infectious anemia, pernicious anemia, tumor of the bone-marrow, or acute leukemia.

(6) Mixed-cell Leukemia.—The term *mixed-cell leukemia* should also be discarded. It was first applied to chronic myelogenous leukemia, in which the number of myeloblasts was very large. These cells were confused with lymphocytes. It is now realized that such a condition is not infrequently characteristic of exacerbations of chronic myeloid leukemia, and of the acute myeloblastic type.

(7) Pseudoleukemia.—Under the title of pseudoleukemia are grouped conditions in which the tissues change as in leukemia without producing any characteristic blood-picture. Some of these are doubtless manifestations of leukemia in an aleukemic stage, while others are undoubtedly due to tumors of the lymphoid or marrow tissue.

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HODGKIN'S DISEASE

Definition.—Hodgkin's disease is an affection characterized by painless progressive enlargement of the lymph-nodes, often accompanied by fever and, in the late stages, by cachexia and anemia. The spleen is frequently enlarged.

History.—Hodgkin in 1832 described for the first time a peculiar group of cases presenting multiple swellings of lymph-nodes. Somewhat later similar cases were recognized in France and Germany, and in 1865 Wilkes named the condition "Hodgkin's disease." It was distinguished from leukemia by Wunderlich. During the history of the disease it has been variously designated as "pseudoleukemia," "lymphosarcoma," "adenie," and "generalized lymphadenoma." In Germany at the present time it is usually called "lymphomatosis granulomatosa" or "lymphogranulomatosis"; in England and this country, Hodgkin's disease.

Incidence.—Hodgkin's disease is widely distributed over Europe and America. The disease occurs most frequently in the second or third decades, and though individuals over fifty years of age are rarely affected, the disease has been seen at the age of eighty. Men are affected more frequently than women.

Etiology.—The cause is still obscure. Though it has been considered from time to time as a new growth, the weight of evidence at present is in favor of regarding the disease as an infectious granuloma. Sternberg believed it to be a peculiar form of tuberculosis, but the negative results which have subsequently been obtained by animal inoculation with lymph-nodes, the characteristic histological picture, and the absence of tubercle bacilli all lead to the conclusion that the disease is not tuberculosis. In rare instances the two conditions may co-exist. The significance of the Gram-positive granular rods, first described by Fränkel and Much, is uncertain. Bunting and Yates have cultivated a Gram-positive diphtheroid bacillus from the lymph-glands, which, upon inoculation into animals, gave rise to a chronic inflammation of the lymph-nodes. It has not been possible, however, to transmit the disease to animals by direct inoculation of tissue. Monkeys and even chimpanzees have not been found to be susceptible.

Morbid Anatomy.—Lymph-glands.—The anatomical picture which this disease presents at autopsy is often very striking. When the glandular involvement is wide-spread great collections of tumors are seen in the neck, thorax, axillæ, retroperitoneum, mesentery, and the inguinal regions.

Usually, however, the process is not so extensive. The cervical nodes are most frequently enlarged on either one or both sides. Chains of enlarged glands may extend into the supraclavicular region and run beneath the clavicles to form masses under the pectoral muscles. The superior mediastinal and bronchial nodes may be involved and occasionally form large tumors, pushing aside muscles, displacing the trachea, and compressing the esophagus and blood-vessels or protruding into the pleural cavities. Occasionally the lungs are invaded. The retroperitoneal nodes often form great chains along the spinal column, or give rise to masses that compress the lumbar or sacral nerves. Occasionally they protrude to form a mass with the mesenteric nodes in the epigastrium, or surround and obstruct the common bile-duct. In the iliac region they may compress the blood-vessels. Wherever the tumors are found their general appearance is much the same. In typical instances the nodes are oval or round, often somewhat irregular, but still presenting a smooth surface. They are not fused, but are separate, even in the largest masses, for the single tumors are held together by loose connective tissue. The color is white, pinkish, semi-translucent gray, or even a delicate cream tint.

The *nodes* vary in consistency; in some instances they are quite hard, in others soft and elastic. The surface of the cut section of the softer glands is pinkish gray, semi-translucent, rather juicy, and either bulging or slightly lobulated.

Occasionally the process may infiltrate the capsules of the nodes and the discrete nature of the separate nodules become to a great extent lost.

The *spleen* is enlarged in about 60 per cent. of the cases by secondary growths. It rarely attains the enormous size seen in leukemia. When the secondary deposits are numerous, the red pulp is streaked and mottled with irregular pearly white or yellow lines and masses, varying in size according to the extent of the process. Infarctions of the spleen occur at times. The *liver* is not so frequently involved as the spleen, but may be the seat of secondary deposits, or may be diffusely enlarged from fatty degeneration. More rarely nodules are found in the *kidneys*. Indeed, it is possible that they may appear in any organ or structure in which collections of lymphoid tissue occur; and growths have been described in the pericardium, pleura, thymus, tonsils, muscles, bone-marrow, periosteum, skin, and gastro-intestinal tract.

Histology.—The first well-marked microscopical changes consist of hyperplasia of the lymphoid cells with active proliferation at the germinal centers of the lymphoid follicles. There is also increased vascularity and proliferation of the reticular endothelium, while the reticulum itself is prominent. The lymph sinuses are dilated and partially filled with cells, among which there are numerous endothelial cells, leukocytes, and eosinophils. Karyokinetic figures are occasionally found in the endothelial cells lining the reticulum.

As the disease advances the normal structure of the node is entirely lost and the microscopical picture shows a reticular network in the meshes of which lie lymphocytes, plasma cells, many eosinophils, epithelioid cells, and mononuclear and polynuclear giant-cells in varying proportions. These elements are not arranged to form any definite structures. One of the most constant and striking features is the polynucleated giant-cell described by Dorothy Reed. In the larger polynucleated giant-cells, which are sometimes

of astonishing size, the nuclei, often from 4 to 10 in number, are heaped together at the periphery, or in the center of the cell, and their general pallor which contrasts with the deeply colored chromatin network, the prominent nucleoli, and their irregular forms give the cells a very characteristic appearance. A second form may have the deeply stained nuclei arranged in the shape of a horseshoe about the periphery of the cells. The tumor at this stage represents the soft type of lymphoma.

In the late stage the predominating feature is the great increase in connective tissue. The cellular parts of the tumor are reduced to small islands lying between the coarse connective-tissue bands. Sometimes small necrotic areas are noted and rarely hyaline degeneration is seen. The late stage represents a much harder tumor than the earlier phases.

Symptoms.—The onset of the disease is occasionally preceded or accompanied by infections about the teeth or of the tonsils. It is not clear that the enlargement of the cervical lymph-nodes is directly associated with these infections.

In about three-quarters of the cases the disease starts with a painless enlargement of one or more groups of *superficial lymph-nodes*, and later pursues a fairly characteristic clinical course. In the remaining quarter the disease presents a much more varied clinical picture and it is possible to differentiate roughly, as Ziegler has done: (*a*) an acute form; (*b*) a localized form; (*c*) a generalized form; (*d*) a mediastinal type; (*e*) a larval form; (*f*) a splenomegalic form; and (*g*) an osteoperiostitic form.

In the more usual form of the disease the patient first notices a gradual enlargement of the *cervical lymph-nodes*. This may be confined to one side, but more commonly there soon follows enlargement of the glands on the opposite side; or the enlargement affects both sides almost simultaneously. In rare instances the enlargement of the axillary or even the inguinal nodes first attracts the attention of the patient. The nodes are not painful or tender. The skin is not reddened over them. The swelling increases slowly and the disease often progresses for several months without producing constitutional symptoms. One symptom, however, which may appear very early is a persistent and severe *pruritus*. Occasionally the disease is almost entirely limited to the cervical region, but, as a rule, the enlargement proceeds from one group of nodes to another, spreading from the cervical or supraclavicular region to the axillary, subpectoral, mediastinal, or even retroperitoneal, mesenteric, and inguinal nodes. The epitrochlear or exceptionally the popliteal nodes may become involved in the general process. As a rule the enlargements are not uniform in size, for the nodes first affected may attain huge proportions, while those involved later are comparatively small. Throughout the disease the separate nodes, even though occurring in large groups, may be felt as fairly well isolated masses; for, unless they become secondarily infected, or are exposed to radium or the *x*-ray, they do not tend to adhere to the skin or surrounding tissues. During the progress of the disease the *spleen* often enlarges, though it rarely reaches a great size. The *liver* may be readily palpable. As the disease advances the patient *loses weight* and begins to present a *cachectic appearance*. The *blood-pressure* is low.

With the progressive enlargement of regional lymph-nodes important structures are compressed and a series of *secondary symptoms* may arise. The trachea and bronchi are frequently involved. This gives rise to the most distressing *dyspnea*. There may be *dysphagia* or *laryngeal paralyses*.

Pain sometimes arises from pressure upon the brachial, lumbar, or sacral nerve plexuses. Compression of veins with *edema* of one extremity is not unusual. An *obstructive jaundice* may complicate the picture, and not infrequently *effusions* take place in the pleural sac or peritoneum. In the later stages edema of the extremities or *anasarca* may develop.

In many instances there is *fever*, sometimes continuous, but of mild degree, rarely exceeding 101° F.; in other instances, the fever fluctuates widely, but is more or less persistent; finally it may show a remarkably remittent character. It is to this *remittent type of fever* that Pel and Ebstein called particular attention. A group of such cases has been studied by McNalty. The course of the fever is almost unique. For weeks and months there may be alternating febrile and afebrile periods. The temperature rises more or less abruptly to 102°, 103°, or 104° F., and persists, often with moderate daily remissions, for three or four days to ten days or two weeks. It then falls and remains normal or nearly normal for days, weeks, or even months before another period of fever takes place. These paroxysms of fever may occur over and over again. In one patient under our observation there were ten remissions of fever during a period of at least a year and three months. These remarkable remissions are more likely to be observed in patients in whom the mediastinal or abdominal lymph-nodes are involved, and present a striking feature in the clinical course of this particular group of cases.

During the progress of the disease *itching of the skin* may be so severe as to become a distressing symptom. Patches of *pigment* sometimes appear upon the skin, or in other instances there is diffuse bronzing. Occasionally *superficial ulcers* are observed and in rare instances *small granulomata* involve the cutaneous tissues.

Once the disease is well established there develops along with the loss of weight, cachexia, and pressure symptoms an *anemia* of secondary type which may actually become grave. The leukocytes do not show constant or distinctive changes. Early in the disease the leukocyte count is normal; in the later stages a polymorphonuclear leukocytosis is common. The most significant variations may be an increase in platelets, an increase in the transitional cells, and at times an eosinophilia.

The disease, if untreated, usually terminates within two or three years in cachexia, from mechanical interference with respiration, or through secondary infections.

There may be several variations from the usual clinical course of Hodgkin's disease. (*a*) In the *acute form* death may occur within a few weeks, or at most months. In one of our cases the duration was less than four months. Ziegler cites cases of death within a month. In this form the enlargement of the lymph-nodes is often remarkably wide-spread, but not very great. (*b*) In the *localized form* the cervical nodes are most often affected. The solitary masses grow slowly for two or three years, and the disease assumes a chronic course. Sooner or later, however, there is an extension of the process to neighboring groups and the disease becomes more or less generalized. (*c*) The *mediastinal type* represents one variety of the localized form in which the mediastinal nodes are especially involved. The patient presents a remarkable picture with all the symptoms and signs of mediastinal tumor—cough, dyspnea, orthopnea, pain, and other evidences of pressure. When there is no enlargement of the superficial lymph-nodes it may be

almost impossible to make the diagnosis of Hodgkin's disease. The radiograph is usually of value in determining the extent of the process. (*d*) The *larval* or *latent form* presents features of great importance. In this type the disease is confined more or less exclusively to the thoracic or abdominal lymph-nodes. The superficial nodes may escape completely. The symptoms are varied and often indefinite. Abdominal pains, jaundice, diarrhea, or effusions into the pleural and abdominal cavities may occur. The spleen and liver are often enlarged. Fever is frequently present. Some of the most pronounced examples of remittent fever occur in this type. The diagnosis is extremely difficult. Cases have been mistaken in the early stages for appendicitis, typhoid fever, and tuberculosis, and in the later stages for malignant growths. (*e*) In the rare *splenomegalic form* the disease is confined principally to the spleen. Whether Hodgkin's disease can be entirely localized in this organ is dubious. In a considerable proportion of all cases of Hodgkin's disease the spleen shows more or less enlargement, but in this type the spleen may reach great size and be the predominant feature. Under these conditions it is extremely difficult to differentiate the disease from splenic anemia or Banti's disease. (*f*) In very rare instances an *involvement of the periosteum* and *bone-marrow* may contribute special features to the course of the disease. If the replacement of the marrow by granulomatous tissue is wide-spread, the anemia may progress with astounding rapidity. In one case with involvement of the vertebræ there was compression of the spinal cord followed by paraplegia.

Diagnosis.—Hodgkin's disease is confused most frequently with tuberculosis and lymphosarcoma; more rarely with lymphocytic leukemia, syphilis, and inflammatory enlargement of the lymph-nodes.

Tuberculosis of the cervical lymph-nodes is often very difficult to differentiate from Hodgkin's disease. In tuberculosis it is important to remember that the glands are frequently tender, that they are often firm and adhere one to the other, and that they are likely to lie deeper in the neck than the tumors in Hodgkin's disease and to be situated beneath the sternomastoid muscle. If the tuberculous glands have softened, or are adherent to the skin, or if an actual sinus has formed, the diagnosis is not difficult. Occasionally in tuberculosis there is a more or less generalized discrete enlargement of lymph-nodes. In such instances there may be fever, and the differentiation is almost impossible without the histological examination of a lymph-node. The presence of tuberculosis elsewhere in the body is often an aid in arriving at a correct conclusion. The most satisfactory method of diagnosis in difficult cases is the excision of a superficial node for histological examination. The tuberculin reaction may be of assistance. An *x*-ray plate may reveal areas of calcification in tuberculous nodes; these do not occur in Hodgkin's disease.

Lymphosarcoma may simulate Hodgkin's disease even more closely than tuberculosis. Lymphosarcoma is perhaps more commonly a cause of mediastinal tumor than Hodgkin's disease. It is less often accompanied by fever. The spleen is not often enlarged. It is well to keep in mind the fact that when lymphosarcoma affects the cervical and submental lymph-nodes the tonsils are frequently involved and greatly enlarged. The exact diagnosis must almost always be made from the histological examination of an excised node.

Though *lymphocytic leukemia* may at first be confounded with Hodgkin's

disease, the blood-picture in the latter disease will immediately determine the diagnosis. Confusion can only arise when one is dealing with those rare cases of leukemia in which for temporary periods the leukocytes approach the normal in number and proportion. The histological changes in the lymph-nodes are distinctive.

There is rarely any difficulty in distinguishing the *gummatous lymph-nodes* of syphilis from Hodgkin's disease. The Wassermann reaction is of assistance in the diagnosis.

Prognosis.—The disease may run a very rapid course, but usually lasts in the untreated cases for two or three years. Of 49 patients, 34 died within two years of onset. By treatment the life of the patient may be prolonged for five or six years. Two patients under treatment lived for seven years. The disease seems to progress slowly even though the enlargement of the lymph-nodes is controlled by applications of *x*-ray or radium. The loss of weight continues and the cachexia slowly progresses; the anemia becomes gradually more severe, and fever may be intermittent or continuous. The immediate prognosis is gravest in those patients who have involvement of the mediastinal and abdominal nodes.

Treatment.—When the disease is strictly localized in a group of cervical lymph-nodes it is sometimes advisable to resort to operation and to remove completely all the affected tissue. Foci of infection about the teeth or in the tonsils should be eliminated. It is not possible to effect a cure by surgical measures, for the disease recurs. For this reason radiotherapy should be employed after operation. In the vast majority of instances operation is inadvisable and resort must be had to radiotherapy.

By the use of *radium* or *x-rays* the lymph-nodes may be greatly reduced in size, and by repeated treatments many of the distressing symptoms caused by pressure from the tumors may be relieved or prevented. As far as is known, this method of therapy does not result in cure, although the patient is spared much suffering. In some instances life seems to have been prolonged by *x*-ray therapy, although Minot's statistics indicate that this result is not the rule.

The only *drug* which is known to produce any beneficial effect is arsenic. This should be administered between the courses of radiotherapy and may be given in the form of Fowler's solution in increasing doses or as sodium cacodylate. It is said that the lymph-nodes may recede temporarily under the influence of arsenic therapy. Tonics may be employed. It is important that the general nutrition should be maintained as well as possible through rest, fresh air, and a nourishing diet.

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PURPURA

Definition.—Purpura is a condition characterized by extravasations of blood into the skin and mucous membranes. The areas of discoloration may vary from the size of a pin-point (petechiæ) to much larger areas, known as ecchymoses.

Occurrence.—Purpura occurs as a symptom of many diseases and may be produced in various ways. It is also a prominent feature of two distinct idiopathic conditions in which it is (1) associated with other exudative lesions, joint and visceral symptoms, and presents no recognized pathology of the blood (*idiopathic purpura*); and (2) characterized by paucity of the blood-platelets and spontaneous hemorrhages from mucous membranes (*idiopathic thrombopenic* or *thrombocytopenic purpura*, purpura hæmorrhagica). A third, less clearly defined, idiopathic form of purpura is known as *purpura fulminans.*

Types.—Symptomatic purpura is usually *simple* and not dependent upon demonstrable disturbance of the blood nor associated with bleeding from the mucosæ. It may result from mechanical causes, venous stasis, or from emboli, as in endocarditis. It may appear in any infectious disease and constitutes the usual exanthem in some, notably epidemic cerebrospinal meningitis. Rashes, like those of scarlet fever and measles, which are usually not purpuric, may be modified by the extravasation of blood into the skin when the infection is severe. The hemorrhages may be seen in many toxic states, including those resulting from the administration of drugs (as copaiba, iodids, quinin, atropin, etc.), and in cachectic patients, in chronic nephritis, and occasionally in diseases entailing degenerative lesions of the spinal cord.

Symptomatic Purpura with Blood Defects.—Purpura may be symptomatic of an abnormality of blood coagulation, as, for example, in prolonged jaundice, severe liver disease, erythremia, and some forms of sepsis. When associated with a marked reduction in the number of blood-platelets in a recognized disease it is known as *symptomatic thrombopenic* or *thrombocytopenic purpura.*

Symptomatic Thrombopenic or *Thrombocytopenic Purpura* (Purpura Hæmorrhagica).—This is associated with bleeding from the mucosæ as in the idiopathic condition. The decrease in the number of the blood-platelets can be brought about by:

(1) Destruction or depression of the activity of their parent cells, the megacaryocytes of the bone-marrow, which occurs in aplastic anemia, and may be idiopathic or result from benzol poisoning, arsphenamin, bacterial toxins, or excessive irradiation with radium or Roengten rays, etc.;

(2) Displacement of megacaryocytes by abnormal cells, as in the leukemias, pernicious anemia, and metastatic tumors;

(3) Destruction of platelets, or their removal from the circulation as, for example, after peptone injection in animals and experimental anaphylaxis, and, according to Weil, in hepatic disease.

Idiopathic Purpura (Primary Purpura).—*Definition.*—A frequently recurrent but rarely fatal morbid state, characterized by purpura, and often associated with other exudative lesions, joint manifestations, and visceral symptoms, but without known abnormality of the blood.

History.—Schönlein described cases with joint manifestations and Henoch those with intestinal crises. Osler clearly showed that the type with purpura, erythema, and allied skin conditions, especially with visceral disturbances, may be considered essentially a clinical entity with protean manifestations.

Etiology.—Children and young adults are usually affected, but no age, sex, or race is exempt. The cause of the condition is unknown. Infection probably accounts for some cases; others, because of their resemblance to serum sickness, and because sensitization to a specific protein is sometimes demonstrable, are thought to be manifestations of allergy. Disorders of the glands of internal secretion may play a rôle.

Morbid Physiology.—The permeability of the small blood-vessels appears to be altered and mechanical factors probably influence the distribution of the lesions. The manifold lesions may be explained by the extravasation of varying proportions of plasma and formed elements of the blood, and by local vascular changes. Every lesion, internal or external—purpura, erythema, or edema according to the blood elements that permeate the vessel walls—is to be considered focal.

The *blood* undergoes no constant changes. Anemia may be present, and the white count is sometimes slightly elevated. The platelet count is not low and the clotting time is essentially normal.

Symptoms and Course.—Idiopathic purpura is divided artificially into various types according to the anatomical distribution of the lesions. Patients may exhibit only purpura (purpura simplex) or there may be concomitant articular symptoms (Schönlein's disease, purpura rheumatica). Some develop symptoms attributable to visceral lesions, those of the intestines causing crises of abdominal pain (Henoch's purpura). Various combinations of skin, joint, and visceral lesions are seen. The patient may exhibit at one time purpura alone, at another urticaria or erythema, while visceral symptoms may develop with or without skin manifestations. Those who exhibit purpura alone are usually free from significant constitutional disturbance. The eruption may be local or general, one or more groups of lesions appearing during the course of several days. The lesions then usually subside, but may recur at intervals of weeks or even years. In others an attack of the disease begins with fever, malaise, and a sore throat, which are followed shortly by polyarticular pains. Days or even weeks later, perhaps after all initial symptoms have subsided, an eruption appears which is often purpuric and commonly associated with urticaria and erythema. Edema is variable in degree, occasionally it is excessive. The arthritic and cutaneous lesions usually subside in a few days, but often recur together or independently at intervals of one to six weeks.

The extravasation of plasma and cells into some viscus may take place whenever there are exudative skin lesions or arthritis, not only in close association with the appearance of such symptoms but often when they are absent. Visceral lesions may develop even years before or after the conditions become externally manifest. They are rarely found elsewhere than in the intestines or kidneys. Fever and malaise generally precede the localizing symptoms. Foci of hemorrhage and edema in the gastrointestinal tract give rise to crises of pain, which is often colicky, to diarrhea, melena, and even to intussusception. Similar infiltration in the kidney may result in hematuria, escape of albumin, and depression of renal function, and thus simulate acute nephritis. Uremic symptoms are exceedingly rare. Severe visceral disturbances seldom last more than a few days,

although, like arthritis, they often dominate the picture. Their intensity fluctuates and their disappearance for weeks is frequent; recurrent attacks sometimes ensue for many years.

Complications are infrequent. Endocarditis has been reported to occur. Enlargement of the spleen frequently develops in children who have had repeated attacks of the disease, but is uncommon in adults.

Diagnosis.—In the presence of purpura or exudative skin lesions, and when the platelet count is normal, the diagnosis is usually simple. If purpura is associated with urticaria, erythema, or edema it is apt to be of this idiopathic variety. Diseases of which purpura may be a symptom must be excluded, as well as *thrombopenic purpura*. The oozing of blood from the mucous membranes in this latter condition and the diminution in the number of platelets serve to distinguish it. *Hemophilia* bears only a superficial resemblance to idiopathic purpura.

The articular pains may suggest *rheumatic fever*, but purpura itself is very rarely associated with this condition. *Scurvy* may lead to confusion, but can be differentiated by careful examination of the dietary history and administration of antiscorbutic substances.

The cases most difficult to diagnose are those in which visceral symptoms develop without skin lesions. The crises of pain so closely resemble those of certain acute abdominal conditions that operation cannot always be forestalled. Operation causes no abnormal hemorrhage because the elements associated with the coagulation of the blood are essentially normal. Symptoms referable to the genito-urinary tract often lead to a diagnosis of *acute nephritis*, and in the absence of skin lesions this cannot be positively ruled out. In every child with severe abdominal pain or hematuria the possibility of idiopathic purpura must be considered and the skin examined for exudative lesions.

Prognosis.—The outlook as to life is nearly always excellent. Individual attacks last ordinarily from one to six weeks, while recurrence at intervals of months or years is not unusual. The mild type is less apt to recur than the more severe form. In no individual case, however, is it possible to determine whether future attacks will occur or what form or severity these may have. Nevertheless, as the individual grows older the disease tends to become milder or to disappear.

Treatment.—There is no specific treatment for the disease. In an effort to alter favorably the endothelial permeability, many substances, including calcium and potassium compounds and animal sera, have been advocated, but none produces striking benefit. Symptoms must be treated as they arise, dietary indiscretions avoided, and good hygiene instituted. If individuals are unduly sensitive to protein, adequate desensitization should be attempted.

Idiopathic Thrombopenic (Thrombocytopenic) Purpura (*Idiopathic Purpura Hemorrhagica, Morbus Maculosus of Werlhof, Pseudohemophilia*).—*Definition.*—Idiopathic thrombopenic purpura is a disease that may be acute or chronic and is characterized by a marked and unaccountable diminution in the number of blood-platelets, spontaneous hemorrhages of the mucous membrane, and purpura.

History.—Werlhof in 1731 first differentiated the condition from other varieties of hemorrhagic disease. In 1887 Denys noted the platelet reduction. Hayem and Bensaude and Rivet called attention to the chronic type of the disease, and Kaznelson first showed the striking results that follow splenectomy.

Etiology.—The cause is unknown. Females are affected more often than males. Young individuals are more often afflicted than older ones. Some cases follow an acute infection, and others are perhaps associated with tuberculosis, but there is no evidence that the condition is produced by a living organism. The chronic form is sometimes congenital or familial and may be of quite a different nature from the acute.

Morbid Physiology.—Postmortem examination has revealed no characteristic lesions. Signs of extensive capillary hemorrhage are the outstanding feature of the disease and are associated with diminution in the number of circulating blood-platelets, a phenomenon which may depend upon their abnormal destruction and perhaps upon a diminished production. Experiments have shown that injection of the serum of rabbits immunized against the platelets of the guinea-pig causes destruction of normal guinea-pig platelets. Moreover, guinea-pigs, which have received inoculations of antiplatelet serum, rapidly develop all the features of clinical thrombopenic purpura. These animals, like the few human subjects studied postmortem, show no decrease in the number of megacaryocytes, which suggests that defective formation of platelets does not necessarily occur in this idiopathic form of the disease. Symptomatic purpura hemorrhagica is often associated with a decreased formation of platelets, and the bone-marrow appears to be implicated in some cases with idiopathic thrombopenic purpura that exhibit varying grades of depression and altered marrow activity. Idiopathic aplastic anemia and certain cases of acute myeloid leukemia might be considered theoretically to represent the extremes.

The circulating blood-platelets are often large and abnormally granular. They may be absent or, as is usual, present in numbers below 100,000 per c.mm. The degree of bleeding is roughly parallel to the fluctuation in the number of platelets and usually ceases when it rises above about 100,000 per c.mm. The bleeding time is prolonged, sometimes for hours, often in proportion to the number of platelets. Striking exceptions do occur. The coagulation time is rarely more than slightly prolonged, but because of the paucity of platelets the loosely woven clot does not retract. The degree of anemia is particularly dependent on loss of blood, but defective blood formation also may be influential. The red and white blood-cell count is usually similar to that seen after mechanical loss of blood, but leukopenia and all signs of marrow depression occasionally supervene.

Symptoms.—*Spontaneous capillary bleeding* from and into mucous membranes is the clinical feature that distinguishes thrombopenic purpura from most other forms. The bleeding may occur into any tissue. It varies from slight oozing from a single source to profuse bleeding from many sources. Hemorrhage from the mucosæ of the nose and mouth is particularly common, and that from the uterus and into the retina frequent. The cutaneous hemorrhages may be extensive, but more often consist of but a few petechiæ, and are rarely associated with other exudative lesions. The vulnerability of the capillaries permits slight trauma to produce ecchymoses.

Fever is the rule in the more acute and severe cases. The spleen may be moderately enlarged, particularly in the chronic type. No other symptoms or signs occur except those attributable to hemorrhages or anemia.

An acute and a chronic form of the disease are recognized.

In the acute type the hemorrhages may begin abruptly without warning

or after some days of debility. In favorable cases the symptoms usually disappear within three weeks, as inexplicably as they arose. In others the course may be short and fatal. The hemorrhages may persist for days and then cease, only to recur after an interval of days or weeks, and may thus render the disease *intermittent* for many months. Such subacute conditions may become very chronic, and patients may live for years without much severe bleeding. It is more usual for the disease to be fatal within a few months. Other patients suffer more or less severe bleeding *continually* for weeks or months, and become gradually exsanguinated or die from a cerebral hemorrhage or the like.

The chronic type of the disease does not usually develop from the acute form. At the time of a brisk hemorrhage the patient often states that for years, or as long as he can remember, he has bruised and bled easily, but not severely, and often has had petechiæ. The platelet count usually remains below normal so the patients continually show some signs of hemorrhage. These may, however, be so slight that for many years the individual gives little thought to the lesions. Intermittently more profound hemorrhages may occur, particularly from the nose and vagina. Rarely the number of platelets fluctuates markedly from well above to much below normal, so that symptoms may be truly intermittent and not continuous.

Diagnosis.—Spontaneous hemorrhage from the mucous membrane and a paucity of platelets are sufficient evidence for a diagnosis of thrombopenic purpura. The idiopathic disease is to be diagnosed after excluding conditions in which thrombopenia is a symptom. *Aplastic anemia* is distinguished by signs of persistent and markedly decreased formation of the three formed marrow elements. Rarely a condition may exist that appears intermediate between aplastic anemia and typical idiopathic purpura hemorrhagica. *Acute leukemia*, even when in the aleukemic phase, will not be confused if a proper blood examination is made and carefully interpreted. The symptom-complex termed *"agranulocytic angina"*—severe oral, especially tonsillar, sepsis with a sudden onset, fever, extreme leukopenia, and other signs of toxic action on the marrow—is to be distinguished.

The joint symptoms, varying exudative skin lesions, and visceral crises common to idiopathic purpura are rare in the thrombopenic forms, while hemorrhages from the mucous membrane and the characteristic blood pathology of the latter further serve to distinguish these two conditions. *Hemorrhage from telangiectases, easy bruising without spontaneous purpura*, particularly in women, as well as *scurvy*, need cause no confusion, as in these conditions there is no paucity of platelets and the patients present quite a different symptomatology.

Chronic thrombopenic purpura has often been confused with *hemophilia*, but these conditions can be easily differentiated as indicated in the chapter on Hemophilia.

Prognosis.—It is impossible to state in a given case whether a patient will succumb shortly or live the expected number of years with or without one or more mild or severe attacks. If a given attack does not show signs of abatement within a few weeks an unfavorable outcome is probable, but death or, much less often, recovery may be delayed many months.

The chronic type shows less tendency to permanent recovery than the acute, although some patients apparently recover even after five or six years, while others die. The disease may last a lifetime, but the condition tends

to become gradually worse. The above statements apply to cases receiving no special form of treatment other than transfusions of blood. The influence of special therapy on prognosis is given below.

Treatment.—Patients should take a nutritious diet, avoid fatigue, and be in the sunlight if possible. Perhaps certain foods, especially those that aid regeneration of hemoglobin, can beneficially affect the blood-platelets in purpura hemorrhagica. Complications such as focal sepsis and disorders of the glands of internal secretion must be treated as occasion permits, but surgery, except for splenectomy, should be avoided when the blood-platelet count is low.

Splenectomy, because of its recognized influence in stimulating the output of blood-platelets and its possible effect in decreasing their abnormal destruction, has recently been shown to have a strikingly beneficial, possibly curative, effect in *chronic* cases. There has been a uniformity in the success of this operation. The operative mortality is very slight. Symptomatic cure has occurred in nearly every case. Its permanency is yet to be learned, although numerous patients who underwent the operation a few years ago continue to remain well. The blood-platelets usually increase in numbers very rapidly after removal of the spleen, and are abnormally abundant. Their histological character also tends to change favorably. After about a week the platelet count falls, to remain, usually for at least many months, at about the normal level. The number of these cells tends, however, to be low, and in some patients there is never more than a slight increase of these elements. Even in such chronic cases, serious bleeding has not recurred, although petechiæ and epistaxis have appeared. Transient slight hemorrhages, chiefly petechiæ, have also recurred after splenectomy in some other cases when the number of blood-platelets was not reduced. Great variation has been reported concerning the recovery of retractibility of the blood-clot. This function is apt to be delayed and may not return simultaneously with the rise of the blood-platelet count. These facts suggest that the increased number of blood-platelets is only one factor in the arrest of the purpuric manifestations. Exactly how extirpation of the spleen achieves at least temporary cure and the arrest of gross hemorrhage is not understood.

It is generally granted that splenectomy is indicated in chronic idiopathic purpura hemorrhagica, but the consensus of opinion is against splenectomy in the acute type, which is probably a totally different disease. The operation is, of course, contra-indicated in symptomatic thrombopenia, and it is wiser not to attempt it when the diagnosis is doubtful. Each case must be considered individually. One must not act hastily, and should recall that many patients with the chronic form live for years with relatively insignificant symptoms, and that spontaneous improvement can occur. For subacute conditions of a few months' duration splenectomy is probably desirable.

Since various forms of the *light-rays* can increase the number of blood-platelets, irradiation of the spleen with small doses of Roentgen rays has been advised in purpura hemorrhagica. It is often without effect, but may benefit the patient somewhat. Increases in the blood-platelet count and a distinct decrease in bleeding have occurred in some of our patients simultaneously with tanning of their skin by sunlight. Sooy and Moise have just reported striking clinical improvement and an increase in the number of blood-

platelets in purpura hæmorrhagica following exposure to a mercury-vapor quartz lamp, and perhaps time will prove that such therapy accomplishes as much as splenectomy.

Other special forms of treatment are entirely symptomatic; the most important are those which check hemorrhage. Though local applications of styptics and thromboplastic substances, as well as injections of the latter, may occasionally aid in controlling loss of blood, *blood transfusion* is undoubtedly the most satisfactory method of doing this. Transfusion may be resorted to when the bleeding or anemia is severe. Transfusion of an adequate amount of blood relieves anemia and usually causes cessation of bleeding for from three to six days, the length of life of the transfused blood-platelets. Repeated transfusion may tide the patient over until his own peripheral blood-platelets become normal. This certainly can be done in symptomatic thrombopenic purpura resulting from partial aplasia of the marrow due to benzol poisoning. *Per se,* however, transfusion appears to have no permanent influence on the course of the disease. If patients require operation, a suitable blood donor should be at hand for several days in case transfusion may be necessary.

Purpura fulminans, first described by Guillot, is a rare variety of purpura, which occurs particularly in young children. The etiology is unknown, although overwhelming infection may perhaps be the cause. The onset is sudden, with high fever. Cutaneous and subdermal hemorrhages are very extensive and death takes place usually in less than sixty hours. The platelet count is reported as normal, and hemorrhage from the mucous membrane is not a feature. Patients with known infection, such as scarlet fever, who develop acute thrombopenic purpura, may cause confusion.

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Thrombopenic Purpura

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HEMORRHAGIC DISEASE OF THE NEWBORN

Definition.—Hemorrhagic disease of the newborn is a self-limited disturbance of unknown etiology occurring only in the newborn and characterized by spontaneous hemorrhages which may occur in any tissue of the body.

History.—The disease was first adequately described by F. Minot in 1852. In 1908 Lambert demonstrated the therapeutic effectiveness of injection of human blood, while later Welch, Schloss and Commisky added further data to our knowledge.

Etiology and Morbid Anatomy.—The disease occurs in about 1 per cent. of all newborn infants. It is not recurrent, and is usually manifest before the fourth day of life and does not develop after the tenth.

The cause is not known and the pathological physiology is obscure. The coagulation time of the blood is usually prolonged, the clot retractile, and the platelets present in at least normal numbers. The bleeding time is rarely abnormal. Except for extravasation of blood and the results of hemorrhage postmortem examination is negative.

Symptoms.—Failure to nurse, fretfulness, subnormal temperature, and even prostration may precede the hemorrhage. Jaundice is often present. The spontaneous bleeding causes ecchymoses, which may be the only sign of loss of blood. Bleeding often takes place from the umbilical stump and intestines. Hematomata and bleeding from instrumental abrasions are common. Less frequently there is intracranial hemorrhage or bleeding from serous surfaces, kidneys, or vagina. The loss of blood from a single source may be slight, but the total amount lost may be sufficient to produce symptoms of marked anemia.

Diagnosis.—It must be borne in mind that the coagulation time of the

blood is somewhat longer in infants than in adults, and that the former bruise readily from pressure. Many cases of *intracranial hemorrhage* supposed to be due to hemorrhagic disease of the newborn are undoubtedly the result of trauma. At this age *melena due to ulcer* is seldom seen. The usual forms of *idiopathic purpura* do not occur in infants, but the *purpura and hemorrhages of syphilis or pyogenic infections*, though rare, must be differentiated from the manifestations of hemorrhagic disease of the newborn. The hemophilic baby rarely bleeds during the first few weeks of life, and melena, a feature of hemorrhagic disease of the newborn, is rare in hemophilia.

Prognosis.—The outlook for untreated infants is grave; over 50 per cent. die within a few days. When human blood is injected early the prognosis is vastly better, and a very high percentage of patients recover rapidly. Once the manifestations of the disease have disappeared there is no recurrence.

Treatment.—Human blood in some form should be administered as soon as the diagnosis is made, and the injection should be repeated if the bleeding does not cease. Intravenous transfusion of blood is the most effective procedure. Although 30 to 80 c.c. of blood usually suffice, more may be required if the anemia is severe. Intraperitoneal transfusion (Sipperstein) also accomplishes the desired effect. Almost equally good results follow intramuscular or subcutaneous injection of human blood if transfusion is not made necessary by the loss of much blood. Several doses of from 10 to 30 c.c. administered every four to eight hours cure many infants, but a sufficient amount of blood must be given in each case to check bleeding.

Other treatment is symptomatic and depends on the needs of the individual case.

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HEMOPHILIA

Definition.—Hemophilia is an hereditary disease in which the coagulation time of the blood is much prolonged. The disease occurs practically only in the male, but is transmitted only by the female. A marked tendency

to hemorrhage throughout life is characteristic. Bleeding sometimes occurs spontaneously, but usually follows trauma, even when the injury is trifling.

History.—There are passages in the Talmud which indicate that the ancient Jews knew of the disease. Consbrush in 1793 and Rave in 1796 described a case. It was J. C. Otto of Philadelphia who brought attention to the condition by his excellent descriptions published in 1803 and 1805. Bulloch and Fildes' monograph is a classic.

Incidence and Etiology.—The etiology of hemophilia is a mystery. The disorder once started is transmitted to males from generation to generation through the female. Hemophilia is apparently a sex-character linked to a single male chromosome. Its incidence follows the laws of Mendelian inheritance. The female conductor transmits the condition to about two-thirds of her male offspring, while about one-third of the female offspring are not conductors. Cases reported in females are usually proved unauthentic. If a male hemophilic should marry a woman capable of transmitting the disease it would be possible for their female children to be hemophilic. The fecundity of the females of "bleeder" families is peculiarly great, and among their offspring there is an abnormal predominance of males, who never transmit the disease. Hemophilia appears to be largely confined to the Teutonic race.

Morbid Anatomy.—Postmortem examination shows that the organs are entirely normal except for the results of hemorrhage.

The Blood.—The numerical counts of the formed elements are normal except after hemorrhage. The number of blood-platelets is never diminished. The delay in both coagulation and prothrombin time is typical, but varies from time to time in the same case. The cause of the delay in coagulation time has been the subject of much study, and the multiplicity of terms used in discussing the problem has caused confusion. It is evident, however, that there is a fundamental alteration in the physical chemistry of the coagulation factors; this has been described as a shortage or qualitative defect of prothrombin, an increase in the quantity of antiprothrombin, changes in calcium ionization, etc. The platelets of hemophilic blood are much less able to initiate coagulation than are those of normal blood. The blood may manifest the reclotting phenomenon, but the clot, once formed, seems firm and retracts normally.

Symptoms.—The essential symptom of hemophilia is hemorrhage following trauma which would not normally cause bleeding. The injury may be very trivial: spontaneous hemorrhage is rare. The bleeding, which often lasts many hours and sometimes days, tends to be of a persistent oozing nature, and may lead to profound anemia or be fatal, though death rarely results from the first loss of blood. The condition usually becomes evident in early childhood, but may not be apparent until later. The tendency to bleed and the degree of bleeding vary in the same and different individuals. The hemorrhage may be external, internal, or into joints. Although pin-pricks do not cause bleeding, scratches may initiate serious hemorrhage. Thus the veins and ears may be punctured with impunity, indicating that the bleeding-time is normal. Obstinate epistaxis is frequent. The cutaneous lesions are in the nature of bruises; that is, they are hematomata, not purpuric spots. Hemorrhages into and about joints are common and may do no lasting harm, but they usually cause destruction of bone and hypertrophic changes, which must be carefully distinguished from the manifestations of tuberculosis of the joints. Internal hemor-

rhages, including those into the muscles and joints, may cause pain and fever.

Diagnosis.—Obstinate hemorrhage is more often due to local injury or disease than to abnormalities of the blood, and the mere fact that bleeding persists does not justify a diagnosis of hemophilia. The diagnosis depends on the family history, the occurrence of repeated bleeding—usually protracted and from more than one location—joint manifestations, and the coagulation time of the blood. Mild, atypical, or "sporadic" cases are rare and may not be suspected until some accident or operation takes place. In such cases the coagulation time of the blood may be delayed but slightly and the abnormality demonstrated only by making a particularly careful test on venous blood.

Hemophilia is to be sharply differentiated from *purpura hæmorrhagica*, especially from the chronic idiopathic form. This latter disease occurs in either sex, and is rarely congenital or familial. The condition of the blood in these two diseases is very different. In hemophilia the physiologically defective platelets are present in at least normal numbers, the bleeding time is normal, and the firm clot retracts; in purpura hæmorrhagica the number of platelets, physiologically normal, is much decreased, the bleeding time is prolonged, and the clot is non-retractile and soft. In the latter condition, the coagulation time is usually not far from normal instead of being prolonged as in hemophilia. Purpuric skin lesions and truly spontaneous bleeding are evidences of purpura hemorrhagica, and not of hemophilia. Other forms of purpura in which the blood findings are essentially normal need cause no confusion.

Hemorrhagic disease of the newborn is neither familial nor recurrent, and develops only in the first few days of life—a time when the male hemophilic baby seldom bleeds. *Melena* is rare in hemophilia. The blood in *hereditary multiple teleangiectasis* or *familial epistaxis* and *hereditary hemoptysis* and *hematuria* is normal, and these conditions as well as scurvy are readily distinguished from hemophilia.

Prolongation of the coagulation time is not pathognomonic of hemophilia, but occurs also in sepsis, nephritis, liver disease, jaundice, and polycythemia among other abnormal states. It is rarely as marked in these conditions, however, as in hemophilia.

Prognosis.—Hemophilia tends to be fatal before the subject attains adult life. The tendency to bleed seems to diminish gradually in the relatively few individuals who live beyond maturity. Few patients reach adult life without suffering some disabling deformity of the joints. Hemorrhages may be of many degrees of severity, but the patient's past experience and the character of the disease in other members of the family forecast the outcome. If the manifestations are mild the condition will probably not become worse.

Treatment.—The *prevention* of hemophilia is a problem of eugenics. The *course of the disease* cannot be fundamentally altered. Hemophilic individuals and male children of tainted stock must be guarded from traumatism, and must know of a suitable blood donor in case transfusion is necessary. General principles of hygiene should be carefully followed. Fresh cephalin and various tissue extracts (tissue fibrinogen (Mills)) enhance clotting, but when given by mouth yield no striking results. A diet rich in meat may possibly exert a beneficial influence on the blood.

The *joints* should receive treatment similar to that of chronic arthritis in order to prevent deformity.

In case of hemorrhage the patient must have absolute quiet. Morphin may be necessary. The blood of hemophilic patients eventually clots and the hemorrhage tends to stop spontaneously; consequently treatment varies according to the severity and location of the bleeding. The special measures to arrest hemorrhage consist of local application or intramuscular and intravenous injection of coagulants and blood transfusion. *Tissue-juice extracts* are most suitable for local use and the patient should always keep such substances close at hand. Numerous patent preparations are purchasable, but in emergencies fresh meat tissue is serviceable. The injection of such extracts and the liberation of such substances by irradiation of the patient with Roentgen rays may perhaps be of value. The desirability of transfusion varies in each case, but this form of treatment is more often unnecessary than necessary. When loss of blood threatens life, transfusion of enough blood (usually 800 c.c.) to restore the coagulation time and the plasma volume to approximately normal is necessary. The effect of transfusion on the abnormal clotting mechanism and thus on the disease is only temporary, yet it is of great value in checking hemorrhage. About three days after transfusion the clotting time of the patient's blood returns to the length before transfusion. One or more transfusions, however, can hasten coagulation for a period sufficiently long to permit healing and stop hemorrhage. Hemophilics can undergo a surgical operation without serious hemorrhage if a large transfusion of blood is given directly beforehand. Further transfusions should be given while the wound is healing and repeated when bleeding appears.

The use of protein sensitization in the treatment of hemophilia is noteworthy. The *non-sensitive* patient is given 3.0 to 4.0 c.c. of sheep or horse serum subcutaneously. After ten days he will usually be sensitive and should then receive about 0.2 c.c. of the same serum intradermally. As the skin reaction becomes positive, the coagulation time of the blood often falls, and if bleeding is in progress it will probably stop. The effect may last for days or many weeks. The skin reaction does not desensitize the patient, so that he is constantly ready to react to other intradermal injections of the protein solution. These may be given as often as desired to check bleeding when it arises.

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ERYTHREMIA

(*Polycythemia (rubra) vera, Splenomegalic polycythemia, Vaquez's disease, Osler's disease*)

Definition.—Erythremia is a chronic, slowly progressive, eventually fatal disease of unknown origin, characterized by excessive erythroblastic activity of the bone-marrow, which induces a persistent polycythemia and splenomegaly. The increase of erythrocytes usually leads to a red cyanotic appearance of the skin, an erythrosis (Lundsgaard), an increase in the viscosity and in the total volume of the blood, and distention and engorgement of capillary vessels.

History.—Vaquez in 1892 described a case, but general knowledge of erythremia remained lacking until Osler drew attention to it in 1903.

Incidence.—Erythremia is rare. It occurs in all races, in either sex, at any age, but especially in individuals about fifty years old. Some cases are familial, others apparently congenital. The blood of members of the patient's family may contain an abnormally large number of red blood-cells while the individuals remain free from symptoms.

Etiology.—This disorder of red blood-corpuscle formation is comparable to that of white blood-cell formation known as *chronic myelogenous leukemia*. The cause of neither is known, but both may be considered as neoplasms of the hemopoietic tissue, especially the latter.

Morbid Anatomy.—There is a striking increase in the quantity of active red bone-marrow which replaces the normal yellow marrow. The microscope permits demonstration of hyperplasia of not only the red cells but also the white cells and megacaryocytes. An abundance of immature forms may be present in the blood, some of which are undifferentiated or abnormal. The basal metabolism is often high when the formation of blood is augmented. Extramedullary formation of blood is unusual. Actual myeloid transformation of the spleen and other organs may occur. The splenic enlargement is usually caused by hyperplasia of the pulp and distention with blood. Anemic infarcts are common and thrombosis is not rare, a fact which may lead to such a condition as perforation of the stomach. Extreme vascular engorgement of all organs is characteristic. The increased blood volume, the physical character of the blood, and the impeded circulation may lead to degenerative changes in the vascular system.

The Blood.[1]—The total volume of the blood in typical cases is much increased, that of the plasma only slightly. The red cell count bears no direct relationship to the blood volume. The proportion of cells to plasma may be increased threefold. This causes an increased viscosity so that grossly the blood, which is abnormally dark red, appears thick and sticky, and the corpuscles settle in the plasma very slowly. This physical condition of the blood often causes the coagulation time to be slow and the clot to be non-retractile in spite of the normal number of platelets.

As a rule, the percentage of hemoglobin ranges between 125 and 150. As the need of the body is no greater than normal, the venous blood is abnormally rich in oxygen. The red cell count is usually 7,000,000 to 11,000,000 per c.mm. The color index is low, sometimes strikingly, and achromia may consequently be marked. The red cell count and percentage of hemoglobin may vary considerably from time to time, not only because of local conditions, but also because of fluctuations in production and perhaps in destruction. Anerythremic phases occur, and anemia may develop.

The abnormal activity of the marrow is reflected in the peripheral blood by the presence of abnormal and increased numbers of immature red cells, bone-marrow leukocytes, and often platelets. The abnormality of the red cells frequently consists in only a slight variation in size and the appearance of an occasional polychromatophilic cell. The number and proportion of macrocytes and microcytes vary. Unevenness in the depth to which the cells stain is a feature. The white cell count is often 15,000 per c.mm., sometimes much higher. The blood may resemble that of myelogenous leukemia. There may be an increased output of urobilin, microcytosis, and certain alterations of the plasma and the red cell fragility which suggest that the increased destruction of blood is compensatory. The age variation of the red cells is shown by their increased resistance in hypotonic salt solutions.

Symptoms.[2]—The *onset* of erythremia is insidious. The symptoms, which are largely directly referable to polycythemia, often do not appear until engorgement has taken place in even the smallest vessels. Some symptoms are attributable to increased metabolism. Lassitude, increased sweating, loss of weight, headache, vertigo, tinnitus, surging and congestive sensations, dyspnea, and various gastro-intestinal symptoms sometimes associated with gastric achylia are common. The typical red cyanosis, most obvious in the face and ears, may be the patient's first complaint. The peculiar color may be absent and the polycythemic patient may even be pale. Changes in position, external temperature, and mood often cause striking fluctuations in color. The vascular distention and engorgement is also shown in the capillaries of the nail-fold, by the bluish-red color of the tongue, and by congestion of the mucosæ, conjunctivæ, and retinæ. Irritability, depression, and forgetfulness are common. Slight palsies of cranial nerves are not unusual. Hemorrhages from or into any part are common, so that apoplectic seizures are not rare. The enlarged spleen often reaches to the umbilicus, and may be associated with a dragging sensation as well as pain. Neuralgia-like pain in the extremities and mus-

[1] A colored plate of the blood of erythremia is shown in the Amer. Jour. Med. Sci., 1923, clxvi, 469.

[2] A colored picture of a patient with this disease is shown in Fig. 29 in "Bedside Hematology," by Gordon R. Ward, 1914, W. B. Saunders Co.

cular spasms are sometimes striking. Swelling of joints is rare. Cardiac failure may be manifest. The heart is often not enlarged, although slight hypertrophy and some increase in rate is not unusual. The blood-pressure is sometimes elevated. Kidney function may be impaired, usually temporarily, by engorgement, infarction, or hemorrhage. Pulmonary emphysema, arterial degeneration and its varying results, erythromelalgia, and pigmentation of the skin sometimes occur.

There are atypical cases of erythremia, some of which are congenital and some of which begin in early life. Erythremia in elderly patients with high blood-pressure, usually with renal disease, but without splenic enlargement, has been described by Geisbrock and Hess. Polycythemia of this type seems to be secondary.

Diagnosis.—The diagnosis depends upon the recognition of a persistent, absolute polycythemia, for which there is no obvious cause. The appearance of the patient and the splenomegaly should render diagnosis simple. The *erythrocytosis* or *secondary polycythemia*, which occurs with circulatory stasis from chronic cardiac disease—particularly congenital—and chronic pulmonary disease (emphysema), must not lead to confusion. The cyanosis characteristic of these states, as well as that due to methemoglobin and CO-hemoglobin, should be distinguished from the erythrosis of erythremia. The saturation of the arterial blood with oxygen in polycythemia due to cardiac or pulmonary disease is less than in erythremia. Confusion must not arise from the relatively slight increase of red cells that result from numerous causes, such as residence at high altitude, and from the administration of certain drugs and exposure to some poisons. *Splenomegaly* due to syphilis or portal thrombosis is occasionally associated with an increased number of red cells in the blood. In erythremia and myelogenous leukemia pathological activity of all marrow elements may occur, so that rarely it may be difficult to determine which of these two conditions was primarily present.

The gastro-intestinal symptoms and those referable to the central nervous system, heart, kidneys, and special sense organs may lead to an incorrect diagnosis of local primary disease.

Prognosis.—The course of the disease is chronic, and there are spontaneous remissions and exacerbations. It is eventually fatal, though death is often produced by other causes. After the development of definite symptoms the duration of life is seldom less than four years. Some patients live twice as long, and others for even twenty years or more. Death may occur during a sudden exacerbation of cyanosis, or as the result of vascular complications, especially cerebral thrombosis or hemorrhage, and cardiac failure. Adequate treatment by modern methods will probably permit a more favorable diagnosis.

Treatment.—The patient must lead a life that does not permit intensification of symptoms. He should avoid mental and physical strain, extremes of temperature, and overeating, especially of meat. Repeated bleedings may give temporary relief.

Irradiation of the long bones and any large mass of blood in the body with short-wave-length Roentgen rays or radion inhibits the formation of blood. Such treatment has definitely benefited some patients when given in adequate, large, repeated doses. Its effect is temporary, not without danger, and, as time passes by, the therapy often becomes ineffective. Serious de-

pression of the white-blood-cell-forming tissue of the bone-marrow must be avoided by observations on the peripheral blood. In this disease irradiation of the spleen alone is unsatisfactory. Splenectomy is contra-indicated. Treatment with benzol has been tried, but is dangerous and without value. It decreases the formation of white blood-cells much more than that of the red blood-corpuscles.

Recently *phenylhydrazin hydrochlorid*, because of its ability to destroy red blood-corpuscles, has been shown to be an efficient therapeutic agent in the treatment of erythremia. The patients who have been adequately treated with this drug have shown a uniform decrease of the hemoglobin percentage and red cell count, and great improvement of all symptoms. Time will determine the full value of phenylhydrazin, but its proper use offers these patients the best treatment known. The drug must be given cautiously in doses determined by the needs of the patient. It is slowly eliminated, partly in the urine which may appear dark brown; has a cumulative action and toxic effect on the liver; and may cause severe anemia. Too much is dangerous, too little, ineffective, but an amount to produce the desired result may be given safely. Acetylphenylhydrazin may be less toxic and equally useful. Following the administration of phenylhydrazin the products of red blood-cell destruction increase and may, by causing a rise of the bile-pigments in the plasma, force the marrow to deliver into the circulation increased numbers of leukocytes, reticulocytes, and other immature forms of cells. The peripheral blood must be scrutinized very frequently for these elements and the drug stopped when their numbers increase considerably. The treatment should also be discontinued when the white blood-cell count or the percentage of reticulocytes remains distinctly elevated. Treatment, guided by frequent blood examinations, may begin with 0.1 gm. of phenylhydrazin in capsules per day by mouth and continued until the red blood-cell count has fallen definitely, or until 1 gm. has been taken. The drug should then be discontinued for a few days to observe whether or not there is any cumulative action. If there is not, another gram may be given within the course of about ten days in 0.1- or 0.2-gm. doses. By proceeding slowly it is possible to obtain the maximum therapeutic effect with little if any danger to the patient. When the red blood-cell count and hemoglobin percentage approach normal, 0.1 gm. must be given less frequently. The interval between doses is lengthened: usually about 0.1 gm. once a week will suffice to keep the red blood-cell count within normal limits. Perhaps treatment for a long period of time will necessitate increasing doses. The combination of Roentgen ray irradiation with the use of phenylhydrazin is to be considered. Untoward symptoms are not to be anticipated while the patient is taking proper doses of the drug. A sense of oppression in the neck and throat may perhaps be due to it. It is desirable for physicians to consult the current literature and the references below before prescribing phenylhydrazin.

George R. Minot.

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ENTEROGENOUS CYANOSIS

(*Methemoglobinemia, Sulphemoglobinemia*)

The term "enterogenous cyanosis" was introduced in 1902 by Stokvis, who described a case of chronic cyanosis, without cardiac or pulmonary lesions, or evidences of drug poisoning. Spectroscopic examination of the blood showed the presence of methemoglobin. Since then over 20 other cases have been reported. The cyanosis depends on the partial replacement of the circulating hemoglobin by the relatively more stable pigments methemoglobin, or sulphemoglobin, which can be demonstrated by careful spectroscopical examination. Because of the difficulty of distinguishing sulphemoglobin from methemoglobin, there is a question as to which pigment was present in several of the cases first reported.

Etiology.—The cause of this rare condition is unknown. Attempts to explain the methemoglobinemia or sulphemoglobinemia as the result of absorption of toxic products from the intestinal tract are unsatisfactory. Cure of the associated intestinal condition apparently causes the disappearance of the cyanosis in the majority of cases, but such evidence is at best difficult to interpret. The fact that in one case the blood-culture contained *Bacillus coli communis* is probably of no significance. Boycott's discovery of methemoglobinemia in rats in association with an infec-

tion by *Gaertner's bacillus* is the only experimental evidence that intestinal infection may have a causal relation to the condition. A valuable discussion of the condition has recently been published by Vogel, who reports a case due to the ingestion of sulphur and the absorption of nitrobenzene.

Symptoms.—The two characteristic clinical features are *intense cyanosis* and marked *intestinal disturbances*, both of long duration. Secondary symptoms are weakness, dizziness, headache, and occasional clubbing of the fingers. Dyspnea is usually not a feature. In undoubted methemoglobinemia diarrhea develops, and nitrites are present in the blood. Patients with sulphemoglobinemia, however, usually suffer from marked constipation. No other pathological findings in the blood or body have been reported.

Diagnosis.—The diagnosis of enterogenous cyanosis depends largely on the demonstration of methemoglobin or sulphemoglobin in the blood, and the exclusion of *cardiac* or *pulmonary lesions*, and *polycythemia* or *drug poisoning*, which are the usual causes of cyanosis. It is of particular importance that poisoning by any of the coal-tar derivatives, potassium chlorate, arsenuretted hydrogen, or other known causes of methemoglobinemia or sulphemoglobinemia, be completely excluded.

Treatment should aim to improve the gastro-intestinal condition. No specific therapy is required.

Chester M. Jones.

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DISEASES OF THE CIRCULATORY SYSTEM

Diseases of the Pericardium

ACUTE FIBRINOUS PERICARDITIS

Definition.—Acute fibrinous pericarditis is an inflammation of the pericardium associated with the formation of a fibrinous exudate on the serous membrane. The lesion may not pass beyond this stage (*pericarditis sicca*), but in some cases the process progresses, and a serous, serosanguineous, or purulent exudate may form (*pericarditis with effusion*).

Etiology.—Pericarditis is probably never a primary disease, although it occurs occasionally when a primary disease or focus of infection cannot be discovered. It is associated with a large number of conditions. *Acute rheumatic fever* is one of the diseases in which acute pericarditis is most frequently seen. It is a complication which is generally encountered within the first two weeks of the disease. It occurs at times in *chorea*. *Focal infections* play an important part in the etiology of many cases of pericarditis of obscure origin. The primary focus may be situated in any part of the body, but is most often found in the *tonsils*, *sinuses*, or *teeth*. Pericarditis also occasionally develops as a complication of the *acute infections*, particularly *pneumonia* and *scarlet fever*. It is seen not infrequently in connection with *septic processes*. It may be a direct extension of an empyema, a mediastinitis, subdiaphragmatic abscess, trauma (stab wounds, etc.), and may develop in the course of puerperal infection, osteomyelitis, gonococcal infection (gonorrheal arthritis), and septicemia of all sorts. The *tubercle bacillus* is also an important cause. The disease may appear when all the serous membranes become inflamed (polyserositis), in the course of a general miliary tuberculosis, or in association with pulmonary tuberculosis; it develops less commonly when other parts of the body, such as the bones or lymphatic glands, become tuberculous. In the later stages of *chronic diseases* pericarditis is a frequent complication. This is particularly true of *chronic nephritis*, in which there is often a terminal pericarditis. It is not uncommon in advanced *diabetes mellitus*, *gout*, and other chronic disorders. An inflammation of the pericardium may occur as a *direct extension* from an *inflammatory focus in the heart muscle*. It is a rare complication of acute leukemia, acute anemia, purpura, lues, and actinomycosis. It may be associated rarely with malignant metastases in the heart.

Males are somewhat more susceptible than *females*. The disease occurs at all ages; during earlier life it is most often associated with the rheumatic cycle and scarlet fever, while later it commonly accompanies Bright's disease or other chronic disorders.

The *micro-organisms* most frequently found in the exudate are the *tubercle bacillus*, the *pneumococcus*, and the various *pyogenic organisms*. *Typhoid* and *paratyphoid bacilli*, *influenza bacilli*, the *Bacillus aërogenes capsulatus*, the *diphtheria bacillus*, and the *colon bacillus* have rarely been found.

Morbid Anatomy.—Acute fibrinous pericarditis is the simplest and most benign type and is, fortunately, that most frequently encountered. The thin, fibrinous exudate which forms roughens the normally smooth serous surfaces. The quantity of this exudate varies; often only a small area of the pericardium is involved, while at times the process may be more generalized. Not infrequently the entire pericardium becomes inflamed. Adhesions usually form between the two serous surfaces.

Symptoms.—As pericarditis is probably always secondary to disease elsewhere in the body, it is necessary to limit the discussion of symptoms to those due to the pericardial lesion. Often, particularly in the aged, no symptoms appear which are referable to the pericardium, and the disease may be overlooked entirely until death, or be detected only by the presence of the friction-rub.

Although in children and adults the *pain* is generally more or less severe, it may be absent, especially if the patient is elderly. There may be only a slight discomfort in the precordium, but the pain is often sharp and not unlike that of acute fibrinous pleuritis, being aggravated by coughing, deep breathing, or change of position. It is usually localized in the precordial region, but may be referred or radiate to other parts of the body. Reference of pain to the abdomen is due to involvement of the diaphragm, and since it may be associated with all the signs of acute abdominal disease, sometimes leads to unnecessary laparotomy. When radiating into the neck or left arm, the paroxysms of pain at times suggest angina pectoris.

Fever is generally present, except in the aged and debilitated, but as the primary disease is so frequently febrile, it is often impossible to determine to what extent the elevation of temperature may be attributed to the pericardial lesion. The temperature rarely rises above 102° F. except in cases where fever already exists, though in children the elevation of temperature may be more marked, particularly in rheumatic cases.

Physical Examination.—*Inspection* of the patient reveals nothing unusual. *Palpation* may reveal a friction fremitus due to the rubbing together of the roughened pericardial surfaces; this is usually felt only when the friction is loud and pronounced. A slight, weak friction sound cannot, as a rule, be detected by palpation. Fibrinous pericarditis in itself causes no changes in the size of the heart which are demonstrable by *percussion*. *Auscultation* yields the most important, and, not infrequently, the only evidence of a fibrinous pericarditis. The friction-rub is a to-and-fro sound, close to the ear, which corresponds to systole and diastole, and varies greatly in intensity in different cases and often in the same case. The timing of the sound differs from that of a to-and-fro valvular murmur, in that it does not begin immediately after the heart sounds and generally overlaps them. It may be only a slight, scratchy noise, perceptible with some difficulty and easily overlooked, or an intense, grating rub, in rare instances audible without a stethoscope a few inches from the chest wall; at times the sound resembles the creaking of new leather, the *bruit de cuir neuf* of the French. The murmur may be heard at one visit, and be absent at the next; not infrequently it persists only a few hours, but it may recur, with increased intensity. It is, of course, stopped when a fluid exudate *completely* separates the layers of the pericardium. The rub is most frequently heard over the right ventricle in the fourth and fifth spaces close to the sternum; it is,

however, often encountered at the base of the heart or at the apex. In rare instances it may be heard posteriorly in the left thorax. In a recent case the rub was so intense that it was audible over the entire thorax, both anteriorly and posteriorly. At times the intensity of the friction is augmented by pressure with the stethoscope. Unlike endocardial murmurs, pericardial friction is not transmitted in definite directions. Change of position of the patient may alter the intensity of the rub considerably. It is important to differentiate a scratchy or crepitant quality of the heart sounds, particularly the first, in the tricuspid area, which is encountered in a small percentage of normal hearts. Its constancy, the more definite timing with the heart sounds, the fact that it is unaffected by pressure with the stethoscope, and the lack of fever or other symptoms permit distinction.

Diagnosis.—The friction-rub is pathognomonic of the disease, but since it is often present for only a few hours, repeated examination of the heart is necessary. Difficulty arises in the diagnosis when there is intense pain without friction-rub at the onset.

A *pleuropericardial friction-rub* should not be mistaken for a pure pericardial rub. The sound has, in addition to the to-and-fro rhythm, definite intensifications associated with the respiratory cycle, which may be temporarily abolished by cessation of breathing.

The normal alteration of the *tricuspid sound*, already mentioned, must be differentiated.

Prognosis.—The prognosis in acute fibrinous pericarditis is good provided the disease does not progress beyond the stage of fibrinous exudation. Adhesion of the layers of the pericardium by organized fibrinous exudate is a common sequel.

Treatment.—Rest in bed is the essential element of treatment. The patient should be supported in the position in which there is least pain, sitting, recumbent, or on the side. Application of an ice-bag to the precordium or of strips of gauze frequently dipped in ice-water often affords relief. In some instances, when the pain is severe, codein or morphin may be required. As the disease is usually secondary to infection elsewhere in the body, treatment of the primary disease is of course important. Foci of infection should be removed when possible.

Roger S. Morris.

PERICARDITIS EPISTENOCARDICA

Definition.—Pericarditis epistenocardica is a disease which occurs in elderly people, and is characterized by sudden, agonizing substernal pain, fever, a pericardial friction-rub, usually transitory, and signs of cardiac decompensation.

Etiology.—The condition is encountered more frequently in males than in females and is uncommon in patients less than fifty years of age. Like angina pectoris, it usually attacks professional and business men, and is relatively uncommon in general hospitals. A definite etiology has not

been determined. It seems not unlikely that at times focal infection may be responsible. Arteriosclerosis is commonly associated with the condition.

Morbid Anatomy.—Thrombosis of a coronary artery or one of its branches is found at autopsy. Secondary degenerative changes in the heart muscle supplied by the occluded artery result in softening and thinning of the wall of the ventricle (myomalacia cordis); and generally a fibrinous pericarditis is found limited to the involved area. Aneurysm of the heart may be a sequel. In spite of the thrombosis of the coronary arteries, collateral circulation may be established and healing follow.

Symptoms.—The syndrome has been well described by Gorham, who has observed 6 cases, in 3 of which the diagnosis was confirmed at autopsy.

The disease begins characteristically with sudden, agonizing pain, usually substernal, which frequently radiates to the left arm. According to MacKenzie, fibrinous pericarditis *per se* is painless and the pain, when it occurs, is due to myocardial involvement. The paroxysm of pain is decidedly longer than that of ordinary angina pectoris, often lasting several hours, and is followed by pain or soreness over the heart which may persist for some days. The pain in some cases is referred to the upper abdomen, and may resemble that due to such acute diseases as perforated gastric or duodenal ulcer, acute pancreatitis, or acute cholecystitis. There are evidences of shock, the patient becomes ashy gray, the skin moist, and the pulse rapid and easily compressible. Laparotomy has been performed in such cases. The blood-pressure falls during the attack.

Fever, usually of moderate degree, comes on within twenty-four hours, as a rule, and persists for four or five days. *Restlessness* may be extreme, but the mind remains clear. A *neutrophilic leukocytosis* may be present.

A *to-and-fro pericardial friction-rub*, frequently of light intensity, develops within the first few days; it is generally transitory, lasting a few hours, often recurrent, and localized over a small area. Gorham considers it the most important and characteristic single sign of the syndrome and one easily overlooked unless repeatedly sought.

The *evidences of cardiac decompensation* vary. There are generally present tachycardia, arhythmia (fibrillation at times), an increase of relative cardiac dulness, especially to the right, the disappearance of a systolic murmur which was present before the attack, or the appearance of a murmur of relative insufficiency, and edema of the lower extremities; in fact, all the manifestations of circulatory failure may be present.

Diagnosis.—The syndrome is fairly distinctive. In a patient past middle life, with stenocardia, fever, myocardial insufficiency, and a to-and-fro pericardial friction-rub, there can be little doubt as to the diagnosis. The greatest difficulty is encountered when the pain is referred to the abdomen, and it is in such cases that careful and repeated examination of the heart is generally the means of determining the true nature of the disease.

Diaphragmatic pleurisy, with pain referred to the abdomen, may simulate pericarditis epistenocardica, especially when there is myocardial insufficiency. The absence of a pericardial friction-rub, the frequent presence of pain referred to the border of the trapezius, the limited movement of the diaphragm on the affected side, or the presence of adhesions as revealed by fluoroscopical examination, usually suffices for the differentiation of diaphragmatic pleurisy.

Prognosis.—The prognosis is always extremely grave. The patient may survive an attack, but the outlook is not hopeful. Occasionally, though exceptionally, the subject survives several years.

Treatment.—The treatment is entirely symptomatic. For the pain, full doses of morphin should be given. Inhalations of chloroform may afford some relief. Nitroglycerin dissolved on the tongue (doses of gr. 1/100 repeated, if necessary, every ten minutes until 10 or more are taken), gives some relief at times, especially to patients with hypertension. Usually, however, the pain persists more or less severely despite all efforts to alleviate it.

Rest in bed during the acute stage is essential, and physical exercise should be resumed very gradually and with great caution. Overexertion should be avoided.

A light, nutritious diet, preferably given in small amounts at frequent intervals, is desirable. Gaseous distension of the stomach and intestines is to be prevented. The bowels should be kept moving freely.

ROGER S. MORRIS.

PERICARDITIS WITH EFFUSION

Definition.—Pericarditis with effusion is an acute inflammation of the pericardium, during the course of which a fluid exudate collects in the pericardial cavity.

Etiology.—The disease is not a primary disturbance, but is secondary to some other pathological process. Acute fibrinous exudation may be followed by effusion; and tuberculosis of the pericardium is commonly associated with effusion of fluid. The disease may be secondary to pulmonary infection or to panserositis; it accompanies tuberculosis in other parts of the body less frequently. It is often seen in sepsis; not a few cases are associated with empyema; in one case pericarditis with effusion was discovered at autopsy after the patient had gradually failed following operation for empyema of the left pleura. The pericarditis which was encapsulated and purulent escaped notice at the physical examination because the pus pocket was entirely restricted to the posterior part of the heart. Effusive pericarditis is often a complication of pneumonia. Subdiaphragmatic abscesses, no matter what their cause, may extend to or rupture into the pericardial sac and set up acute inflammation.

Morbid Anatomy.—The visceral and parietal layers of the pericardium may be covered with various quantities of fibrin; this may be so abundant as to form a coarse, shaggy coat which at times greatly interferes with aspiration of fluid from the sac. The fluid exudate may be of several kinds —serous, serosanguineous, hemorrhagic, seropurulent, or purulent—but whatever its nature, flakes of fibrin are generally found floating in it. The quantity of fluid contained in the pericardial cavity varies very much; in some cases only 100 or 200 c.c. may be found, while in others 1.5 or 2 liters may distend the sac. In contrast to transudates the inflammatory

exudates have a relatively high specific gravity (1.017 +) and usually a total protein content of more than 30 gm. per liter. The fluid is clear (serous) or cloudy, according to the number of cells which it contains; in purulent exudates a thick, creamy pus may be found, which at times has a putrid odor. The cytology of the exudate varies with the nature of the fluid; in serous exudates there is usually a preponderance of lymphocytes, although at certain stages of the disease polynuclear neutrophils may be more numerous; there are always endothelial cells, singly or in plaques. In the bloody fluids, generally associated with tuberculosis, malignancy, purpura, or senility, red corpuscles are more or less abundant, while in the purulent exudates pus-cells are so numerous as to completely dominate the field; many of the cells are necrotic and stain very imperfectly.

Bacteriology.—Cultures of the serous exudates are not infrequently sterile; guinea-pig inoculation demonstrates at times that they contain *Tubercle bacilli.*

In the purulent exudates pyogenic organisms are generally demonstrable—*Pneumococci, Streptococci,* or *Staphylococci.* Other organisms are less commonly isolated.

Symptoms.—The onset of pericarditis with effusion is seldom abrupt, often very insidious, and as the disease is so frequently secondary to serious trouble elsewhere in the body, it may not alter markedly the general condition of the patient.

The disease may often cause little or no local discomfort. If *pain* develops, it may be localized or referred, as in acute fibrinous pericarditis and pericarditis epistenocardica. Its intensity varies; there may be merely a dull, heavy feeling of discomfort or the most severe stabbing, cutting, or constricting pain.

The *expression of the face* may be anxious. The *skin* becomes ashy gray, cyanotic, and covered with cold perspiration, especially when there is pyopericardium.

Dyspnea is usually, though not invariably, present, and is often extreme. Generally, the *alæ nasi* dilate on inspiration. The patient is apt to lie on the left side, but when the quantity of the effusion is large, the breathing becomes more labored, there is orthopnea, and the patient is unable to recline with comfort.

There is often marked *restlessness* and *insomnia* and, at times, active delirium or coma. Infrequently, symptoms of mania or melancholia necessitate constant watchfulness on the part of attendants.

Any noteworthy distention of the pericardial cavity may *irritate nearby nerves.* Irritation of the recurrent laryngeal nerve may lead to laryngeal paralysis and aphonia; irritation of the vagus, as well as pressure on the esophagus, to difficulty in swallowing; pressure on the phrenic nerves, to vomiting or hiccup. The veins of the neck may often be markedly distended. An aggravating cough, usually without expectoration, may result from pressure on the trachea and bronchi.

The *pulse rate* in pericarditis with effusion is high, as a rule, and irregularity is common. Heart-block or auricular fibrillation may be associated, although they are not produced by the pericardial lesion *per se. Pulsus paradoxus,* a condition in which the pulse becomes weak or imperceptible at the height of inspiration, also occurs and is probably merely an exaggeration of the normal respiratory arhythmia, though there may not

be the expiratory slowing of the pulse. Pulsus paradoxus is inconstant and not pathognomonic.

The *fever* is usually that typical of the primary disease, but aggravated somewhat. It may be continuous, but is more often remittent or intermittent; with the latter type, which is especially frequent with purulent exudates, there may be profuse sweating.

Physical Examination.—Inspection may show a fulness or bulging of the precordium, especially in children. The apex impulse is often not visible, particularly if the effusion is large; but in one patient in the Cincinnati General Hospital the apex was distinctly visible and palpable in the normal position throughout the disease, although the quantity of effusion was large. This was explained at autopsy by the presence of localized, fibrous adhesions between the visceral and parietal layers of the pericardium over a small area of the right ventricle. Fulness of the interspaces may be noted and, at times, edema of the chest wall, particularly in pyopericardium. The expansion of the left side of the chest is lessened by large effusions. Bulging in the epigastrium may be due to depression of the left lobe of the liver. The superficial veins of the neck, thorax, and upper extremities may be distended.

Palpation.—Friction fremitus generally disappears as fluid accumulates, but even when there is considerable effusion it may be continuously found at the base with the patient erect. As the quantity of fluid increases, the apex impulse usually becomes less and less distinct until, finally, it is no longer palpable, unless, perchance, the heart is fixed to the anterior chest wall by localized adhesions (*vide supra*). A vanishing apex impulse is one of the important signs of collection of fluid in the pericardium, particularly when accompanied by an increase in the relative cardiac dulness. Occasionally, when the apex is no longer palpable in the recumbent posture, it may be felt if the patient is sitting or leaning forward. The diaphragm phenomenon of Hoover—a lagging or standstill of the left costal border in the epigastrium during inspiration—can often be observed when the quantity of the effusion is large. The left lobe of the liver may be depressed.

Percussion.—Dulness at the base of the heart in the first and second interspaces, shifting with change in posture of the patient, is the most valuable single sign of pericardial effusion. It is most satisfactorily demonstrated by Hoover's method of direct percussion with the middle finger. To comprehend clearly the significance of this physical sign it is necessary to remember that the pericardial pockets about the great vessels at the base of the heart fill with fluid relatively early, as Morris and Bader showed in experimental injections of ascitic fluid into the pericardium of fresh cadavers, and as we have been able to demonstrate in pericarditis with effusion. Consequently, a widening of the area of relative dulness in the first and second interspaces to right and left of the sternum may be the first evidence of effusion, and may precede widening of the right and left borders of cardiac dulness. Effusions of moderate or large size constantly increase the width of the area of relative dulness at the base of the heart, except in the rare instances when localized adhesions between the two layers of the pericardium prevent accumulation of fluid at this point. The dull area in the first and second interspaces should be mapped out with the patient first recumbent, then erect. To obtain results, which are so far as possible objective, the eyes of the examiner should be averted or closed

during percussion. A narrowing of the dull area in the erect posture is indicative of effusion in the pericardial sac. This phenomenon, doubtless due to shifting or change in position of the fluid, is demonstrable not only by percussion but also by fluoroscopy.

Likewise, the area of relative cardiac dulness to right and left of the heart shifts with effusion, the change being just the reverse of that found at the base of the heart. Thus, when the patient sits up, the relative dulness extends further to the right in the fourth interspace and further to the left in the fourth and fifth interspaces, than when the patient was recumbent.

Much undue emphasis has been laid upon the fact that the cardiohepatic angle is obtuse in pericarditis with effusion. This sign is often lacking, even when the effusion is large; in fact, the cardiohepatic angle is usually a right angle and may be acute, even if the effusion is massive. Study of radiograms of pericardial effusions, indeed, lead one to expect that the angle will be acute or, at most, about 90 degrees, and experimental and clinical observations confirm this.

With large effusions there may be impairment of the percussion note in the left axilla and the left back near the angle of the scapula and at times diminished breath sounds and weakened fremitus. In one patient, the physical signs were so suggestive of pleural effusion that a needle was inserted at the angle of the left scapula and a syringeful of fluid withdrawn. Soon thereafter, when a liter or more of serous fluid was taken from the pericardium, the physical signs disappeared. Subsequent events made it practically certain that the fluid obtained at the first puncture came from the pericardium and not from the pleura. Instead of being diminished or distant, the breath sounds may be bronchial in character, and the spoken and whispered voice increased about the angle of the scapula, the result, no doubt, of compression of the lung. This, with dulness, may arouse suspicion of pulmonary infiltration.

Auscultation.—A friction-rub, present at the onset, may disappear as fluid accumulates. At times it persists at the base, especially when the patient sits erect. As the fluid is absorbed, the rub may return, and often, immediately following paracentesis, a loud rub reappears. When the patient is under observation from the onset, it is generally noted that, as the apex impulse becomes weaker and is finally lost, there is a coincident diminution in intensity of the heart sounds. The layer of fluid apparently acts as a muffler. With a large effusion the sounds may be very distant or scarcely audible. The sign is inconstant. The second pulmonic sound may be accentuated. Occasionally those at the base are more distinct in the erect than in the recumbent posture.

Radiography.—The radiographic findings[1] in pericarditis with effusion vary with the amount of fluid present. A moderate pericardial effusion causes general enlargement of the cardiac shadow. This condition is difficult to diagnose and it is only when the pericardium is distended that the appearance is characteristic. The heart assumes a pear-shape or water-bottle form, and extends upward to the first or second rib, not only on the left but also on the right side. It frequently occupies a median position, the shadow on the right being as large as that on the left side. The normal cardiac curves are obliterated, especially along the left border, and the heart

[1] The writer is indebted to his colleague, the late Dr. Carl F. Little, for the paragraphs on *x*-ray examination.

contours consequently are longer than normal. There is marked broadening of the shadow immediately above the diaphragm.

Fluoroscopical examination reveals that the cardiac pulsation is absent or only faint. This sign is of the greatest importance, and immediately differentiates pericardial effusion from chronic hypertrophy and chronic dilatation.

It is remarkable that the size and shape of the pericardial shadow changes only slightly after aspiration of a considerable quantity of fluid.

Differentiation between fluid in the pericardium, pleural effusion, chronic hypertrophy and dilatation of the heart, and, rarely, acute dilatation of the heart, must be made. *Pleurisy with effusion* usually presents no difficulties in diagnosis. The shadow observed is not symmetrical and is usually on one side at the base. The cardiac shadow remains normal and the pulsation is visible. In *chronic hypertrophy and dilatation of the heart* the shadow is not so typically pear-shaped, and does not extend so high along the sternal margins nor so low in the fifth and sixth interspaces on the right. Moreover, the cardiac measurements in the sitting and in the recumbent positions do not undergo the changes so characteristic of pericardial effusion. Fluoroscopical examination reveals a well-marked forceful pulsation. Rarely, *acute dilatation of the heart* presents great diagnostic difficulties. In this condition the shadow observed is very similar to that of pericardial effusion, and the pulsation of the heart is very faint, if visible at all. The shape does not change with position in acute dilatation, but does almost always in pericardial effusion.

In children less than one year old the shadow of an *enlarged thymus gland* merging with that of the heart may closely resemble that characteristic of pericarditis with a moderate amount of effusion. An enlarged thymus does not change shape with change of position. *x*-Ray therapy decreases the size of the shadow, a fact which, combined with the results of clinical examination, should lead to a proper diagnosis.

Diagnosis.—The diagnosis of pericardial effusion is often quite difficult, especially if the effusion is fully developed when the first examination is made. If the patient can be watched from day to day as the fluid collects, the physical signs usually permit recognition of the condition without much difficulty. In doubtful cases, fluoroscopical examination may aid greatly in diagnosis.

Dilatation of the heart, when extreme, may present difficulties in physical diagnosis, particularly in stout persons. Osler has summarized the most important differences in the following words: (*a*) "The character of the impulse, which in dilatation, particularly in thin-chested people, is commonly visible and wavy. (*b*) The shock of the cardiac sound is more distinctly palpable in dilatation. (*c*) The area of dulness in dilatation rarely has a triangular form; nor does it, except in cases of mitral stenosis, reach so high along the left sternal margin or so low in the fifth and sixth interspaces without visible or palpable impulse. Dulness, shifting with change of position, speaks strongly for effusion. (*d*) In dilatation, the heart sounds are clearer, often sharp or fetal in character; gallop rhythm is common, whereas in effusion the sounds are distant and muffled. (*e*) Rarely in dilatation is the distention sufficient to compress the lung and produce the tympanitic note in the axillary region, or flatness behind. (*f*) The *x*-ray picture may be very definite, and unlike any form of dilatation or hypertrophy of the heart."

Diagnostic puncture is the means by which the existence of a pericardial effusion may be definitely demonstrated. Various points for the introduction of the needle have been suggested, *i. e.*, the fourth and fifth left interspaces close to the sternum, the costoxiphoid angle, and a point outside the apex. Experimental as well as clinical evidence indicates that the last of these locations is the best. The area of dulness should be mapped out carefully, and a point chosen in the fourth, fifth, or sixth left intercostal space just within the area of dulness. It is, of course, obvious that if the apex impulse is palpable and can be felt within 1 or 2 cm. of the left border of relative dulness, introduction of a needle at this point would be unwise, because of the danger of penetrating the heart. Except when there are adhesions in the region of the apex between the heart and the pericardium, however, an effusion by distending the sac will generally cause the apex impulse to become indistinct or to disappear completely, and will likewise cause relative dulness to extend well beyond the point at which the apex is situated. Under these conditions exploratory puncture can be performed with little or no risk of wounding the heart. It is well, as a rule, to select one of the lower interspaces, the fifth or, if the effusion is large, the sixth. After cleaning the skin with tincture of iodin and alcohol, a sterile needle should be inserted between the ribs about 1 cm. within the outer border of dulness, the direction of the needle being upward, inward, and backward. Contact with the heart is at once apparent, and the needle should be withdrawn until it is free.

If fluid is obtained, part should be placed in sterile containers for culture and animal inoculations, and the remainder saved for determination of the specific gravity, protein content, and cytology. It is advisable to inject not less than 15 c.c. into the guinea-pig if tuberculosis is suspected. A few drops of sterile, saturated, aqueous solution of ammonium oxalate should be added to the fluid to prevent clotting.

Prognosis.—The duration of the disease depends to a considerable extent upon the nature of the exudate and upon the exciting cause. Tuberculous cases and those with purulent exudates are often fatal, whereas there is usually absorption of the exudate in the rheumatic cases. Adhesions between the two layers of the pericardium not infrequently completely unite the heart to the pericardium. In many cases, especially when not extensive, the adhesions do not embarrass the heart action, especially if the heart muscle has escaped serious damage.

Treatment.—The patient must be kept in bed, and should be spared all physical exertion. An ice-bag applied to the precordium often relieves the pain. The diet should be light. The bowels must be kept open and abdominal distention avoided.

If the accumulation of fluid is sufficient to embarrass the heart action, paracentesis should be performed. Great relief usually follows withdrawal of several hundred cubic centimeters of fluid. The operation should be repeated as often as necessary. At times, particularly in the rheumatic cases, the effusion subsides without aspiration, but if the quantity is large, early aspiration is advisable.

If the fluid obtained by puncture is purulent, the ribs should be resected immediately and the pericardium opened in order to allow free drainage of the pus.

Roger S. Morris.

HYDROPERICARDIUM

Hydropericardium is the condition in which a transudate collects in the pericardial cavity.

It is not uncommon at autopsy to find an excess of fluid in the pericardial cavity (25 to 30 to several hundred c.c.). The condition is most commonly encountered in chronic cardiac and renal disease, but it may accompany many chronic disorders. It has been observed in leukemia, in the anemias, etc.

Hydropericardium *per se* usually causes no symptoms.

The *physical signs* depend entirely upon the quantity of transudate in the pericardium. If this is sufficiently large, most of the signs associated with pericarditis with effusion are found. The radiographic findings are also similar in the two diseases.

The fluid is usually clear, pale yellow, with a specific gravity below 1.015 (usually 1.012 or less), and with a total protein content of less than 30 gm. per liter. The cells are chiefly lymphocytes and endothelial cells. Rarely a chyliform transudate is seen.

Roger S. Morris.

HEMOPERICARDIUM

Hemopericardium results from the escape of blood into the pericardial cavity. The hemorrhage may be due to external violence (knife or gunshot wounds); rupture of an aneurysm of the aorta into the pericardium, or of an aneurysm of the heart itself or of a coronary artery; and, in rare instances, to rupture of infarcts of the heart muscle, or to new growths. Generally, a large hemorrhage into the pericardium results in sudden death.

Roger S. Morris.

PNEUMOPERICARDIUM

Pneumopericardium, resulting from the presence of gases in the pericardium, is a rare condition of little clinical importance in civil practice. It may result from penetrating wounds or from rupture into the pericardium from a hollow viscus, as, for example, the esophagus or stomach.

It causes replacement of the relative cardiac dulness by tympany, and if a fluid exudate later collects, peculiar splashing or churning sounds may be heard on auscultation. Hippocratic succussion sounds may be elicited, in addition to those caused by the heart's action. On *x*-ray examination the air within the pericardium is apparent.

If the fluid is purulent, surgical drainage should be resorted to.

Roger S. Morris.

ADHERENT PERICARDIUM; CHRONIC ADHESIVE PERICARDITIS

Definition.—Chronic adhesive pericarditis is a condition resulting from the presence of fibrous adhesions between the pericardium and the heart. Obliteration of the pericardial cavity may be partial or complete. There may also be adhesions extending from the pericardium to the mediastinum, the pleuræ, the diaphragm, and the chest wall.

Etiology.—Following an acute fibrinous pericarditis or a pericarditis with effusion it is not unusual to find adhesions between the visceral and parietal layers of the pericardium. These are often not extensive, result in no permanent damage, and are an accidental finding at postmortem. Occasionally, however, they are more abundant and extensive, the union of the heart and pericardium being complete and the adhesions often binding the pericardium to the pleuræ, sternum, diaphragm, and mediastinal structures. There is often a chronic mediastinitis. The condition is encountered most frequently in adults.

Morbid Anatomy.—The fibrous adhesions are dense and firm in cases of any considerable duration. As the disease is essentially chronic, firm fibrous tissue uniting the pericardium to the neighboring tissues is usually revealed at autopsy. Rarely, there are no adhesions between the visceral and parietal pericardium. The heart is usually hypertrophied and dilated, often to an extreme degree. In a recent case the heart measured 17 cm. from the base to the apex, and 14.5 cm. at its greatest diameter; in another case the greatest diameter was 20 cm. The usual fibrosis of the myocardium may or may not be associated with degenerative change in the muscle cells. The hypertrophy of the ventricles, particularly the left, may be extreme; the wall of the left ventricle in one of the cases just cited was 3.7 cm. thick. Aortic insufficiency is the only other disease in which the heart attains such size. The fibrous overgrowth may extend through the diaphragm and involve the surfaces of the liver and spleen, or it may involve the pleuræ as well as the peritoneum.

Symptoms.—The symptoms produced by an adherent pericardium are primarily those of hypertrophy and dilatation of the heart. It is not, as a rule, until myocardial insufficiency ensues that the patient is troubled subjectively. Then, all of the symptoms of *compensatory failure* may appear—dyspnea, first on exertion, later while at rest; cough; edema of the lower extremities; often swelling of the abdomen (ascites); weakness; and exhaustion. In some cases the cardiac symptoms are more or less in abeyance, and ascites is the most prominent feature (pseudocirrhosis of the liver of Pick). Repeated tapping may be necessary. There is no *fever* except in the later stages, when terminal infections may develop. The *pulse* is that characteristic of the cardiac condition. *Pulsus paradoxus* may be present.

According to E. S. Smith, when the adhesions involve the left ventricle, the first evidences of *circulatory disturbance* are in the pulmonary circulation (dyspnea, pulmonary congestion, etc.), while with involvement chiefly of the right ventricle, the stasis is mainly in the great veins and produces ascites and hepatic congestion. The stasis is generally most pronounced in the portal system.

When there is general involvement of the *serous membranes*, the syndrome may be that of polyserositis, with effusions into the pleural cavities in addition to ascites.

Physical Signs.—Inspection.—On inspection the apex is usually broad, it may be heaving; not infrequently there is a systolic retraction of the interspaces and even of the rib in the neighborhood of the apex. The apex is often displaced downward, being seen in the sixth space, and may be as far to the left as the anterior axillary line. When the patient shifts his position it can be seen that the apex is fixed. This is, however, generally determined more satisfactorily by palpation. There may be noted diastolic collapse of the veins of the neck. Not infrequently, as a result of adhesions to the diaphragm, there may be seen a systolic retraction of the lower ribs (eleventh and twelfth) posteriorly on the left, as Broadbent has pointed out. There may be precordial bulging, and diffuse lifting of the precordium with each systole.

Palpation.—On palpation in the region of the apex the systolic retraction may be detected, but, as a rule, the diastolic rebound or shock is more pronounced. The position of the apex impulse remains fixed and does not shift when the patient changes position. Thus, if the apex is in the sixth space in the anterior axillary line when the patient is on his back, it remains stationary if he turns on his right side. As already noted there may be *pulsus paradoxus*, weakening or disappearance of the radial pulse at the height of inspiration.

Percussion of the heart and great vessels reveals nothing distinctive. There is often an enormous increase in the extent of relative cardiac dulness both to the right and to the left.

Auscultation.—There is nothing characteristic in the auscultatory findings in adhesive pericarditis. The pulmonary second sound is often accentuated. Associated valvular lesions, such as mitral stenosis, may add their distinctive physical signs. Systolic murmurs from relative mitral and tricuspid insufficiencies are common in the later stages with dilatation of the heart. It is said that there may be a well-marked presystolic murmur when there are adhesions between the pericardium and diaphragm. François-Franck has noted that metallic heart sounds may be heard on auscultation over the stomach.

In addition to the physical signs already described there are often evidences of all the phenomena associated with myocardial insufficiency, such as hydrothorax, ascites, swelling of the liver, signs of passive congestion of the lungs and kidneys, and general anasarca.

Arhythmias due to the associated myocardial lesions are not uncommon.

Diagnosis.—The diagnosis in well-marked cases is usually not difficult if the distinctive physical signs are present. At times, however, one sees patients with marked systolic retractions and apparent fixation of the apex, with no adhesions postmortem. The condition may at times be overlooked when ascites is the predominating feature, unless careful attention be given to the physical examination of the heart. A history of a previous attack of pericarditis is important.

Not infrequently pericardial adhesions follow a *pericarditis with effusion* or an *acute fibrinous pericarditis*. These adhesions may be slight in amount or very extensive. Adhesions between the layers of the pericardium alone usually cannot be demonstrated by *fluoroscopy*. In more extensive involvement the pericardium may be attached to the pleuræ, diaphragm, or mediastinal structures. On fluoroscopical examination the presence of adhesions may be observed most accurately during forced inspiration.

If attached to the diaphragm, they prevent regular excursions and produce irregularities at their points of attachment. They restrict the descent of the diaphragm during forced inspiration. The adhesions are often seen at the apex of the cardiac shadow, where the heart and pericardium are more or less fixed. Adhesions develop more frequently on the left side, but may form on either or both sides. Adhesions between the pericardium and pleura are also more frequent on the left side. They appear as small, pointed projections spreading out over the surface of the heart shadow. Under these conditions on deep inspiration the left diaphragm is forcibly pulled up with each contraction of the heart. In E. S. Smith's case the diaphragm was drawn upward 3 cm. This phenomenon corresponds to Broadbent's sign. In cases with extensive pericardial adhesions the cardiac shadow is enlarged as a result of chronic cardiac disease and presents the picture of chronic hypertrophy and dilatation.

Prognosis.—The disease is essentially chronic, and the ultimate outlook depends entirely upon the myocardium and its ability to carry the added burden. It may be able to compensate for years, but sooner or later it fails.

Treatment.—Medical treatment is of avail only when the heart begins to fail. The usual methods for combating myocardial insufficiency should be employed.

Surgical intervention, while not without danger, offers the best hope. The problem, once diagnosis is established, is distinctly surgical, and operation, if undertaken, should be performed before the onset of myocardial insufficiency.

ROGER S. MORRIS.

CALCIFIED PERICARDIUM

With the organization of any inflammatory exudate about the heart, lime salts may be deposited. The extent of the calcification is variable; in some instances it involves the entire pericardium. The signs of an adherent pericardium may be found. More often the condition is latent, and is accidentally found at autopsy or by *x*-ray examination.

ROGER S. MORRIS.

TUMORS

Cancer may metastasize and involve the pericardium. A few cases of *primary sarcoma* of the pericardium have been recorded. *Hydatid cysts* may involve the pericardium, and Cordes has reported a case in which a *dermoid cyst of the mediastinum* ruptured into the pericardial cavity; a clinical diagnosis of pericarditis with effusion was made, the true condition being revealed at autopsy.

ROGER S. MORRIS.

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Diseases of the Heart

SYMPTOMATIC DISORDERS

Certain symptomatic disturbances of the heart are not associated with any demonstrable cardiac disease. The most important of these are *palpitation* and *cardiac pain*, both of which are very common, and are referable to a number of causes, such as disorders of the nervous system, infections, and various forms of toxemia. These symptoms may also be manifestations of organic heart disease, and differentiation between the functional and organic conditions is not always easy.

"Palpitation" is a term used to describe cardiac action which is perceptible to the individual. When mild, the beats are felt within the chest without other sensations. The more aggravated forms of palpitation may be accompanied by real distress. The action of the heart is forcible, often pounding, and the rate may be increased. Irregularities, usually premature beats, are often felt.

Etiology.—By far the most common cause of palpitation is digestive disturbance. *Chronic constipation* with secondary functional alterations in the gastric secretions, *overeating* or *too rapid eating with insufficient mastication*, are frequent etiological factors. Palpitation may also occur when the nervous system is unduly excitable; it is common in hysteria and neurasthenia, at the time of puberty, and during menstruation and the menopause. *Females* are more liable to the affection than males. In another group of individuals the symptoms are caused by various *toxic substances* such as tea, coffee, tobacco, or alcohol, as well as by certain *drugs*, including aspirin

and other coal-tar products. Palpitation is also associated with *organic disease* of the heart, but even then may be of purely nervous origin. In *effort syndrome* it is almost constant. In *hyperthyroidism* it is common.

Symptoms.—In the milder form there are no symptoms except the consciousness of cardiac pulsation. In the most severe cases the patient is aware not only of the pulsations of the heart against the chest wall, but of throbbing of the vessels in the neck and flushing of the face. The heart rate is usually increased and there are signs of distress. Palpitation may be accompanied by epigastric distention and eructation of gas and sour fluid. Attacks of palpitation are often followed by the passage of a large quantity of pale urine.

Physical Signs.—The physical examination of the heart is usually negative. At the most there is only exaggeration of the normal signs, a sharp apical thrust, with a clear, perhaps ringing, first sound, a diastolic shock, and accentuated second pulmonic sound without murmurs, as a rule. At times, however, a functional systolic murmur can be heard either at the apex or over the pulmonic area. The *heart rate* may or may not be increased; it rarely rises to 120. The *action* is regular or interrupted by frequent *extrasystoles*. There is no change in the *blood-pressure*. In nervous individuals the *expression* may be anxious. During digestive disturbances an area of exaggerated tympany may be found over the stomach.

Diagnosis.—Since palpitation is so frequently associated with other pathological conditions, examination of the heart alone is not sufficient for diagnosis. The mental and physical state of the patient must be carefully investigated and a searching examination made for the cause of the cardiac symptoms. The functional neuroses, hysteria and neurasthenia, gastro-intestinal disorders, the anemias, and disturbances of the endocrine glands must be considered possible etiological agents. Pulmonary tuberculosis and obscure foci of chronic infection should also be kept in mind.

Prognosis.—The prognosis depends entirely on the underlying cause. This may be extremely difficult to remove. Palpitation may persist for many years without appreciably affecting the heart itself.

Treatment.—If the palpitation is not due to organic disease, it is first essential to quiet the mind of the patient by the definite assurance that there is no actual danger and that nothing is wrong with the heart. This often gives great relief and frequently allows more willing co-operation in the necessary search for underlying causes.

Digestive disturbances of a functional nature, as well as constipation, should be corrected. Exercise is beneficial unless it is rendered inadvisable by the exciting cause. The effect of discontinuing alcohol, tobacco, coffee, and tea should be determined. The writer has found coffee a more frequent cause than any other single agent. Massage and tepid baths are often helpful.

Heart pain, like palpitation, may be a purely symptomatic disorder. It is felt at, or just to the outer side of the apex, and must be distinguished from pain in this area due to organic disease of the heart or aorta.

Etiology.—Precordial pain is a common accompaniment of angina pectoris, aortitis, aneurysm, and aortic insufficiency; it occurs less frequently with the other forms of endocarditis, myocarditis, cardiac dilatation, and pericarditis. It is, therefore, important to determine the exact

character of the pain, its relation to exertion, excitement, the taking of food, and the direction, if any, of its radiation. In the absence of organic disease of the heart, pain may be the result of digestive disturbance, such as distention of the stomach or colon or of overindulgence in tobacco or coffee. In patients with functional psychoses, in "neurotic" individuals, and in women at the time of the menopause, heart pain may be an annoying symptom. It is one of the usual complaints in effort syndrome. It is more common in *women* than in men and may occur at *all ages*.

Symptoms.—The *pain* may be a constant dull ache or pressure, or may come in attacks of varying length when it is sharp and stabbing. There may be a feeling of oppression, but never the anxiety or distress of angina pectoris. During attacks, particularly in nervous individuals, there are apt to be manifestations of marked nervous excitement—restlessness, talkativeness, or even tossing about in bed. Pain often occurs at night and is more common during rest than on exertion.

Diagnosis.—The heart and circulation are usually normal, but careful questioning about the state of the circulatory, nervous, and digestive systems is necessary, particularly when the patient has passed middle life and is therefore more subject to true angina. It must be remembered that mild attacks of *angina pectoris* do occur and that when diagnosis is uncertain it is better to regard the disturbance as angina than to make light of the symptoms.

Irritable Heart (*Effort Syndrome, Disordered Action of the Heart, Neurocirculatory Asthenia*).—Definition and Incidence.—The various terms used to designate the condition of irritable heart have been applied not to any specific disease of the heart, but to a very definite combination of symptoms referable to the circulatory system. The chief of these are fatigue, dyspnea, and precordial pain. No careful clinical investigation was made of the condition until DaCosta saw some 300 cases during the Civil War. From that time until the recent World War practically no thought was given to the subject, and it was only when large numbers of soldiers with "disordered action of the heart" were sent back from the front to England that the condition was again recognized and deemed worthy of thorough investigation. The work of Thomas Lewis in England, who devised the term "*effort syndrome*" has shown conclusively that the condition is, as far as the circulatory apparatus is concerned, entirely functional. Among the drafted men in our own army the syndrome was frequently encountered, chiefly in men from rural sections, and from the mountainous regions of Kentucky, Tennessee, and West Virginia.

The condition is not confined to soldiers, however, but occurs in *civil life*, in women and children as well as in men. It is much less common in cities than in the country, probably because when an individual recognizes his inability to withstand the strain of competitive life he reduces his activity to what can be maintained with the least effort. A history of frequent change of occupation, each demanding less physical exertion than the last, is commonly obtained. The farm is often the place of last resort.

Etiology.—There are several etiological factors to be considered. The *physically subnormal type of individual* who is unable to do heavy work is often a victim. Such patients are thin and have poorly developed muscles; they are of visceroptotic build and are often of inferior mentality. *Infection* also plays its part. "Effort syndrome" may persist for months after

an attack of rheumatism, tonsillitis, pneumonia, or typhoid; or result from a chronic focal infection in the teeth, tonsils, or other parts of the body. Irritable heart develops in a smaller number of patients who have been restrained from the usual activities of childhood by overzealous parents.

Symptoms.—The most frequent complaint is *shortness of breath* on slight physical exertion. With this goes an unwonted *fatigue*. *Pain* is common, and is referred to the precordial region or felt in the left chest near the apex. It differs from that of angina in that it does not radiate to the neck or arms, and is not of the crushing, boring type, but is a dull, steady ache which subsides with rest. It is not infrequently accompanied by precordial tenderness. Patients are subject to frequent attacks of fainting and dizziness; they complain also of palpitation and excessive perspiration.

Physical Signs.—The *expression* is often anxious, the *hands* are blue and cold, with a coarse tremor, and when the patient is stripped, even in a cool room, *perspiration* runs from the axillæ. The *heart rate* is increased (90–130); the *apex impulse* is diffuse, and sometimes a *coarse thrill* may be felt over the precordium. This is systolic in time, and is due probably to vibrations in the chest wall which are set up by the overactive heart. *Irregularities* seldom occur, but *functional murmurs* are common, the apical or pulmonary systolic being the more frequent. The *response to exercise tests* is poor, the expression often becoming more anxious and drawn; the heart rate increases quickly and maintains the high rate longer than is normal. Occasionally the patient is unable to complete mild exercise tests because of dyspnea and fatigue. The *blood-pressure*, except for being labile, is not strikingly changed.

Diagnosis.—The rapid action of the heart, the accentuation of both sounds, and the thrill at the apex, which may be difficult to time, may confuse the condition with *mitral stenosis;* but if the patient reclines until the heart rate has diminished, the sounds resume a more nearly normal tone and the thrill may disappear completely. The administration of atropin or the inhalation of amyl nitrite, which accentuate both the murmur and thrill in mitral stenosis, has the opposite effect on these signs in effort syndrome. Irritable heart bears a certain resemblance to *hyperthyroidism*, but the absence of enlargement of the gland, the coarse instead of the fine tremor, the marked lack of physical endurance, and the low basal metabolism serve to differentiate the two conditions. *Pulmonary tuberculosis* must always be suspected, and inquiries should, therefore, be made regarding cough, fever, and night-sweats.

Treatment of Symptomatic Disorders.—In all these so-called cardiac neuroses it is important that no suggestion of "heart disease" be given the patient. An attempt must be made to deflect his mind from the heart and to explain the real nature of his condition as clearly as possible. A careful investigation should always be made for an exciting cause, particularly for some focus of infection in other parts of the body. The irritable heart following acute infections responds best to outdoor life, graduated setting-up exercises, and proper hygiene. Those based on hereditary underdevelopment respond most unsatisfactorily to treatment. Hospitalization does harm. No benefit should be expected from the ordinary cardiac drugs.

Henry James.

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CARDIAC ARHYTHMIAS

The cardiac arhythmias are of absorbing and practical interest and have long interested physiologists and clinicians. Osler mentions that the Alexandrian anatomist, Herophilus, during the classic period of Greek medicine (460–136 B. C.), counted the pulse with a water clock and made an elaborate analysis of its rate and rhythm.

The taking of the radial pulse is one of the oldest of the clinical methods of investigation. The moment the normal pulse rhythm is disturbed in any respect, explanation is at once sought in the physiology and pathology of the circulation. Certain grave disorders of cardiac rhythm, however, such as certain forms of heart-block, auricular flutter, and bundle branch block, are not manifest in the radial pulse and can only be demonstrated by graphic instruments of precision, like the polygraph or electrocardiograph.

The clinical interpretation and significance of cardiac arhythmia depends not only on the character of the irregularity but also on data gleaned from the history and general physical and laboratory examination of the patient. That is to say, a given cardiac irregularity found by simple palpation, auscultation, or electrocardiographic or polygraphic examination may assume quite different significance when the patient, for example, is "neurotic"; has just recovered from influenza; has had syphilis; has been taking digitalis; has accompanying precordial pain or dyspnea; has the physical findings of cardiac enlargement; hypertension; edema of the extremities; enlarged tender liver; moisture at the lung bases; hyperthyroidism, etc. In other words, evidence of cardiac arhythmia must be intimately correlated with other important data before diagnosis can be certain.

Classification.—The classification of the cardiac arhythmias changes as increasing knowledge of their mechanism and significance tends to alter pre-existing views. Wiggers' statement that the disorders of cardiac rhythm are due to either disturbance of impulse formation or of impulse conduction provides a physiological basis of differentiation in the light of present knowledge. Wiggers' classification, with one or two slight modifications, is as follows:

CLASSIFICATION OF CARDIAC ARHYTHMIAS

Disturbances of Impulse Initiation

A. Homogenetic Rhythms:
- I. Abnormal sinus rhythms (nomotopic rhythms):
  - (*a*) Sinus tachycardia.
  - (*b*) Sinus bradycardia.
  - (*c*) Phasic sinus arhythmia.
- II. Ectopic rhythms:
  - (*a*) A–V rhythm (junctional or "nodal" rhythms).
  - (*b*) Idioventricular rhythm.

B. Heterogenetic Rhythms:

III. Premature systoles of:
  (*a*) Auricular origin.
  (*b*) Atrioventricular origin.
  (*c*) Ventricular origin.
IV. Paroxysmal tachycardia of:
  (*a*) Auricular origin.
  (*b*) A–V nodal origin.
  (*c*) Ventricular origin.
V. Auricular fibrillation.
VI. Auricular flutter.

Disturbances of Impulse Conduction

VII. Heart-block:
  (*a*) Sino-auricular block.
  (*b*) Auriculoventricular block.
  (*c*) Bundle branch block.
  (*d*) Arborization block.
VIII. Alternation of the heart beat.

Disturbances of Impulse Initiation

HOMOGENETIC RHYTHMS

I. Abnormal Sinus Rhythms.—(*a*) Sinus Tachycardia.—The average rate of the adult human heart, 72 to 78 beats per minute, is an expression of the balance between the relatively rapid rate of impulse formation at the sino-auricular node (the pace-maker) and the inhibitory control of the vagus. Under a variety of conditions when control of the heart beat continues to reside in the sinus node, there is an increase in the pulse rate termed *sinus* or *simple tachycardia.*

Such tachycardias are of *daily occurrence.* They develop after active exercise or prolonged effort, with most fevers, in tuberculosis, hyperthyroidism, emotional excitement, after physiological doses of atropin, in psychoneurotic individuals, during nicotin poisoning, and physical or nervous exhaustion, etc. In contrast to true paroxysmal tachycardia, sinus tachycardias start and cease gradually. They may be transitory, prolonged, or recurrent. Electrocardiographically they appear normal (Fig. 12), except for the increase in rate and a possible increase in the height of *R* and *T* waves (Wiggers).

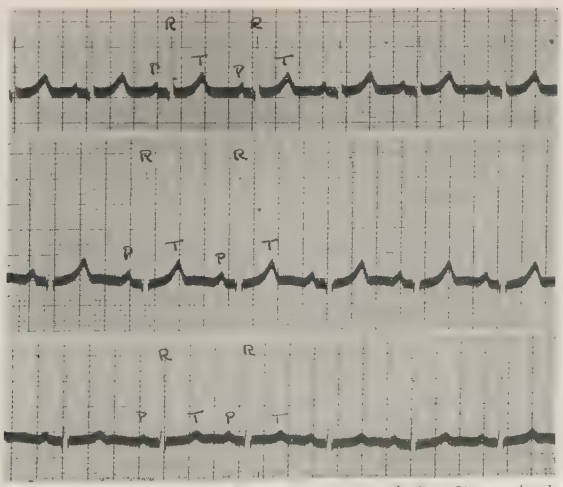

Fig. 12.—Normal electrocardiogram: Leads 1, 2, and 3. P, auricular systole; R-T, ventricular systole; P-R, 0.12 sec.; rate, 88; time marker, 0.2 sec.

They are *caused* usually by transitory diminution of vagus control or temporary stimulation of the sympathetics (accelerator nerves).

As Vierordt's table shows, the *average rate* varies with age:

At birth	130–146
2 years	111–124
4 years	110–111
6 years	99–102
8 years	97– 98
10 years	88– 93
12 years	81– 71
15 years	81– 87

This gradual slowing with advancing years is probably an expression of increased vagus control.

Many of these simple tachycardias are difficult to explain. Certain patients and families are accustomed to a rapid pulse, but many irregularities are evidence of obscure chronic (focal) infections or of early heart-muscle incompetency. Others persist for months or years after an acute infection. The frequent association of a simple tachycardia of this type with chronic osteo-arthritis, chronic infections of the gall-bladder, obesity, etc., is striking. The early stages of subacute or chronic bacterial endocarditis may be ushered in with a sinus tachycardia.

Simple tachycardia of itself demands no *treatment*. Of importance, however, is the diagnosis and treatment of the underlying etiology if such exists and can be found. To give *digitalis* for the tachycardia alone is a serious sin of commission; to omit to give it for the tachycardia which is an expression of an early heart-muscle failure is as serious a sin of omission. Differentiation between the two conditions often calls for the most astute and intensive diagnostic skill. In such instances the inability to decide definitely may justify the administration of digitalis as a diagnostic-therapeutic procedure. A constantly *high metabolic rate* may offer an explanation, even in the absence of a palpable enlargement or adenoma of the thyroid. Apical tooth abscesses, chronic sinus infections, a persistent, moderate leukocytosis, and chronic cough with apical lung dulness often make the diagnosis clear.

(*b*) Sinus Bradycardia.—Slow beats of sinus origin are much less frequent clinically than are simple tachycardias. They often occur in so-called vagotonic individuals; in patients undergoing prolonged rest in bed, especially during partial or complete fasting; during convalescence from the acute fevers, especially influenza, typhoid, and diphtheria; and following prolonged nervous or physical fatigue and exhaustion.

Simple sinus slowing may be of vagal *origin* arising anywhere from the center in the medulla to the vagus endings in the sino-auricular node. Reflexes from eyes and sinuses are said to be causal factors. Sinus bradycardias may also be due to direct toxic action on the sino-auricular node. *Atropin* is useful in differentiating vagal from direct sinus slowing. Certain drugs, notably digitalis, cause slowing both through the vagus and sinus pathways. Anoxemia, asphyxia, and pregnancy are said to be causes of sinus bradycardia (Wiggers). The electrocardiogram of sinus bradycardia is normal with the exception of a possible flattening, notching, or inversion in the *P-wave*, due to origin of the impulse in the lower areas of the sinus node.

Sinus slowing must be differentiated from slowing which occurs in partial or complete auriculoventricular heart-block, nodal or idioventricular rhythm. For this the degree of slowing is important, rates continually below 35 beats per minute usually meaning complete heart-block (idioventricular rhythm), between 40 and 50 partial heart-block (Lewis). Final diagnosis, however, must depend on the polygram or electrocardiogram.

Treatment depends on the cause of the bradycardia. If this is demonstrated to be of clinical importance it should be corrected. The bradycardia itself requires no treatment. Toxic, medicinal, and nervous causes should be relieved.

(*c*) Phasic Sinus Arhythmia (*Juvenile Irregularity; Respiratory Arhythmia*).—Phasic sinus arhythmia which is usually a benign irregularity of the pulse is of greatest importance from the standpoint of misinterpretation and consequent unnecessary treatment. It is a physiological accompaniment of youth and adolescence, and at this period its absence is of more significance than its presence. It is dependent on vagal tone; with inspiration there is temporary lifting of vagal control with increase in rate; with expiration, a deepening of vagus action with decrease in rate. In nervous children this respiratory relationship is often strikingly increased, to such an extent indeed as to cause sometimes an incorrect and alarming diagnosis and prognosis. Sinus arhythmia occasionally accompanies mild digitalis poisoning, unassociated with respiratory rhythm. It may be seen in grave cerebral disease, vagal neuritis, vagal tumors, meningitis, increased intracranial tension, and contraction of the *foramen magnum* (Wiggers). The aged also often show a similar increase in vagal effects (Gilbert).

Diagnosis is usually not difficult; *prognosis* is excellent; *treatment* is not required. The electrocardiogram is essentially normal except for the rhythmic cycles of variations in rate, usually synchronous with respiration.

II. **Ectopic Rhythms.**—(*a*) A-V Rhythm (*Junctional or Nodal Rhythm*). —*Definition.*—Auriculoventricular rhythm is an abnormal cardiac rhythm due to loss of the normal control of the heart by the sino-auricular node, the pace-maker residing lower in the auriculoventricular node, and initiating practically synchronous impulses in both auricles and ventricles.

Incidence.—This is a relatively rare arhythmia occurring only five times among 1200 cases in Hamburger's series.

Pathological Physiology.—This irregularity is said to occur after the use of certain drugs, notably digitalis and atropin, in general myocardial involvement, and during acute febrile diseases (Wiggers). The ability of the normal heart to initiate cardiac impulses in the sino-auricular node lies dormant in other areas of the heart, namely, in the auriculoventricular node, the bundle of His, and certain other portions of the ventricle. The rate of discharge of impulses from these areas is usually lower than that of the sino-auricular node, hence the dominance of the latter under normal conditions. Control by these slower centers of impulse formation is secured when the more rapid sino-auricular node is either destroyed or temporarily held in abeyance by drugs, vagus action, fever, etc., or when the slower center (A-V node) is speeded up by accelerator action. Clinically nodal rhythm is usually seen under the former condition.

The impulse initiated in the auriculoventricular node spreads in both directions to auricles and ventricles, the *time relationship* of the two de-

pending on the exact location of the impulse formation. If the impulse starts in the upper auricular portion of the node the auricle contracts first, but the A-V interval is shortened; if in the center of the node, the auricle and ventricle contract synchronously; if in the lower portion of the node, the ventricle contracts first and the auricle second, a reversal of the normal auriculoventricular sequence. The electrocardiogram in the first instance shows a shortened *P-R* interval with inversion or other anomalies of the *P-wave*. In the second type the *P* is often found embedded or lost in *R*. In the third instance *P* occurs after *R*, usually between *R* and *T* (Fig. 13).

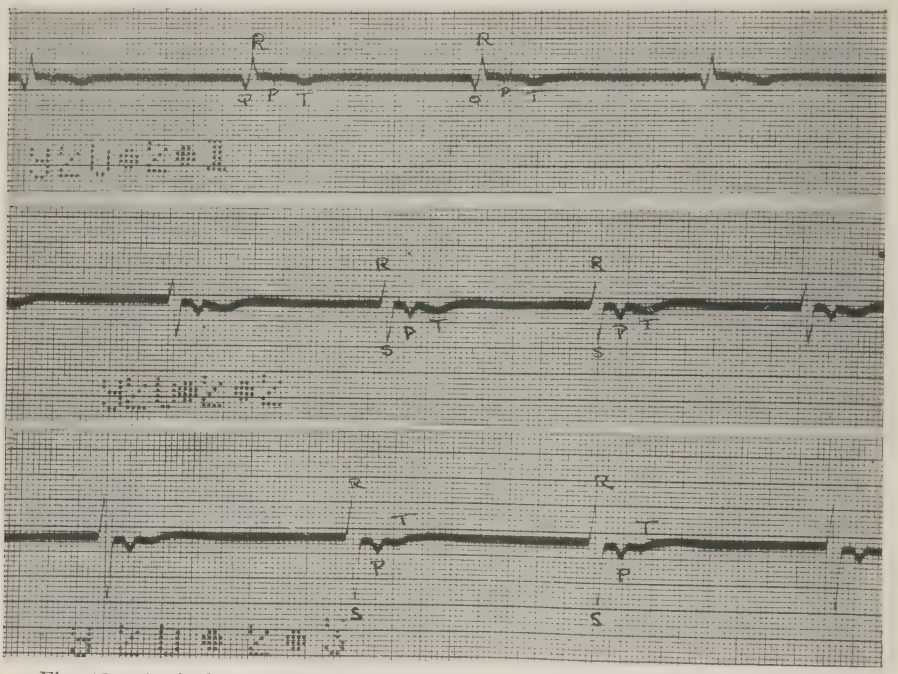

Fig. 13.—Auriculoventricular (nodal) rhythm. Ectopic center located in lower portion A-V node, showing R-P interval, a reversal of the normal A-V sequence; Q-R-P, 0.20 sec.; rate, 37.

The pulse in nodal rhythm is usually regular and slow, 35 to 50 per minute, because of the slower dominant rhythm of the auriculoventricular node. If the nodal rhythm is due to accelerator stimulation the pulse may be rapid.

A *diagnosis* of auriculoventricular rhythm is suggested by a slow regular pulse, final evidence being secured from the electrocardiogram.

Prognosis and *treatment* depend on the etiology. Permanent nodal rhythm is usually indicative of destruction of the sino-auricular node and, therefore, evidence of wide-spread myocardial disease; transient nodal rhythm is usually due to drugs or to toxic or febrile influences.

(*b*) Idioventricular Rhythm.—When auriculoventricular heart-block is complete, the slow regular systole of the ventricle is controlled by a center which usually lies in the bundle of His and gives rise to idioventricular rhythm. The development of such rhythm, therefore, implies the complete cutting off of supraventricular impulses coming down from the

auricle. Inasmuch as this occurs most commonly during complete heart-block, further details of the clinical physiology and pathology of idioventricular rhythm will be discussed with auriculoventricular block.

HETEROGENETIC RHYTHMS

III. **Premature Systoles** (*Extrasystoles; Premature Contractions; Dropped or Missed Beats*).—In addition to the normal systole of auricle and ventricle in regularly beating hearts, any portion of the heart muscle may, under certain abnormal conditions, initiate unexpected bizarre contractions known as premature systoles. These premature systoles, arising in auricular, ventricular, or junctional tissue, occur before the expected regular systole. They do not take place during normal contraction of the particular portion of the heart involved (refractory period) but during its relaxation (diastole). The premature beat is usually followed by the so-called compensatory pause, which, in the case of auricular extrasystoles, is of variable length; in ventricular premature contractions, the pause plus the preceding normal cycle equals approximately the time of two normal heart beats (Krall).

Incidence.—Premature systoles are among the commonest of the pulse irregularities. In a series of 1200 electrocardiograms taken in the heart station at Michael Reese Hospital, 11.2 per cent. were classified as premature contractions. They are said to occur some time in the life of every adult person (Lewis). *No age* or *sex* is exempt. They are perhaps most frequent in neurotic young adults.

Etiology.—Premature systoles depend upon an increased irritability of that portion of the heart muscle responsible for their genesis. This increased irritability may be due to a variety of causes: extrinsic nervous influences (vagus or accelerator nerves); toxic influences (pneumonia, influenza, nicotin, caffein); drugs (digitalis, barium, calcium, chloroform); and nutritional or structural changes in the heart muscle. Under certain other conditions premature contractions are frequent, notably during hypertension, pregnancy, fatigue, emotional excitement, and disease of the gall-bladder. In some cases the etiology may be entirely unknown.

The phlegmatic patient may be unaware of these premature systoles, which may be discovered by the physician during the course of examination. The nervous individual, however, may become very much exercised over these mysterious "twists" and "thumps" which he feels in the region of his heart, and are often most noticeable at night before he falls to sleep.

Symptoms.—Premature systoles of the auricle are said to be "silent"; those of the ventricle cause subjective symptoms. Both types are more frequent in slowly beating hearts. Anything which tends to accelerate the pulse tends to cause them to disappear (unless they are associated with organic changes in the myocardium), exercise for instance, and fever, emotional excitement, or inhalation of amyl nitrite (Lewis).

Palpation of the radial pulse usually reveals the compensatory pause. Occasionally the weak premature beat may be felt. On auscultation the faint premature systole is heard, followed, after a pause, by the loud first tone of the returning normal rhythm. The aortic valve closure is often not heard.

The irregularity due to premature systoles may be the only demonstrable abnormality, or there may be such evidence of complications, as

increased blood-pressure, anginoid pains, dyspnea, cardiac or aortic enlargement, endocardial murmurs, signs of heart failure, etc.

Premature systoles may be transient, recurrent, or permanent; solitary, occurring at great intervals; multiple or frequent; rhythmic, occurring after every normal heart beat (*pulsus bigeminus*); after every second normal beat (*pulsus trigeminus*); or interpolated at regular intervals between every two normal slow beats.

Diagnosis.—The diagnosis depends on the demonstration of some of the characteristics of premature systoles discussed above, plus electrocardiographic evidence.

The clinical significance of extrasystoles would fill an interesting chapter. When due to a transient cause and unassociated with other evidences of cardiac disease they are probably entirely benign; when associated with other findings of circulatory disease, on the other hand, their significance is quite different, the diagnosis and prognosis then depending upon that of the underlying or associated disease. Often these extra beats may be the first warnings of early cardiac involvement, necessitating a more exact study and examination before a final opinion can be given.

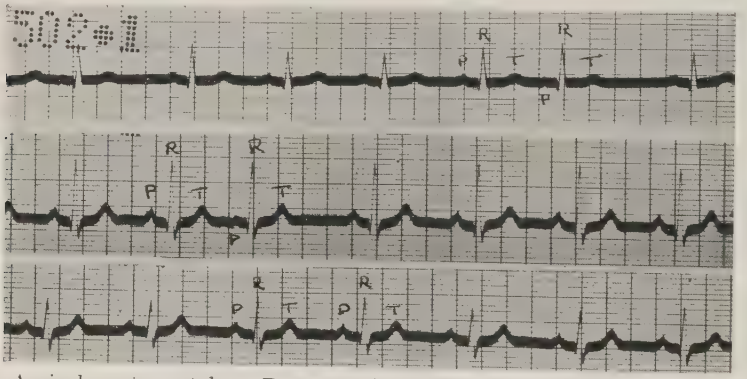

Fig. 14.—Auricular extrasystoles. Premature beats of the auricle are shown in Leads 1 and 2, indicated by "P" below the line, occurring not far from the normal pace-maker.

Treatment should aim to remove the underlying cause. *Bromids* are useful in neurotic persons. *Quinidin sulphate* has recently been used with marked success, probably because of its general depressant action. The dose is a three-grain (0.2 gm.) capsule before meals and at bedtime. *Progressive exercise* and *calisthenics* are said to be useful. When premature beats are not associated with other clinical findings and do not seriously annoy the patient no special treatment is necessary. *Psychotherapy* and reassurance of the patient are often of great value.

(*a*) Premature auricular systoles may arise in any part of the auricular musculature. The electrocardiogram may show normal, premature, anomalous or inverted *P-waves*, shortening of the *P-R* interval, with normal ventricular complexes (Fig. 14). Under certain conditions auricular extrasystoles may not be followed by ventricular contraction.

(*b*) Premature contractions of nodal origin (nodal extrasystoles), which are less frequent than those of auricular or ventricular origin, are due to increased irritability of the junctional tissues. The electrocardiogram shows premature beats with auricles and ventricles contracting synchron-

ously, inversion of *P* with marked *P-R* shortening, *P* absent or buried in *R*, or the presence of *R-P*, that is, a reversal of the normal auriculoventricular sequence as in nodal rhythm.

(*c*) PREMATURE VENTRICULAR CONTRACTIONS are contractions which may arise in any area of either the right or left ventricle. The electrocardiogram shows a large bizarre deflection, usually diphasic in character and widened. Those arising in the right ventricle show the more prominent initial wave below the line in the first lead, above the line in the third. In the left ventricle the reverse is true (Fig. 15). The contour of the deflections varies with the portion of the ventricular area involved. Auricular systoles (*P-waves*) continue uninterrupted, but because of the refractory period of the ventricles following the abnormal extrasystole they may be found either in their normal position, superimposed on or embedded in the ventricular extrasystole, or lost to view (Lewis).

IV. **Paroxysmal tachycardia** is an abrupt, suddenly developing, marked increase in the heart rate, often to double or treble the normal. The

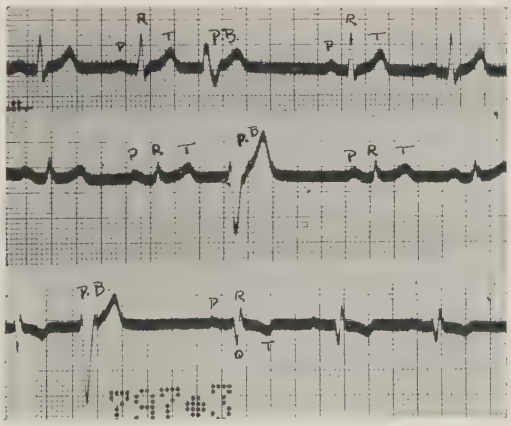

Fig. 15.—Left ventricular extrasystoles (P. B.). These are present in all leads, the abnormal beats being followed by a compensatory pause, succeeding auricular and ventricular systoles occurring in their normal position.

tachycardia persists for a variable length of time, minutes, hours, or days, and terminates with an equally abrupt return to normal. This interesting and dramatic type of arhythmia is fairly frequent, constituting in private practice about 16 per cent. of a series of cardiac irregularities. It is seen frequently in women of advancing years.

Paroxysmal tachycardias are usually divided into three groups—the auricular, nodal, and ventricular—depending on the site in the heart from which they take their origin. They are believed to arise from new ectopic foci of increased irritability which give rise to a series of rapid, regularly recurring, premature systoles. A paroxysm of tachycardia is often preceded and followed by one or more premature beats of which the patient is often aware and which may give warning of the onset.

Symptoms.—The paroxysm itself is usually accompanied by a feeling of faintness of variable degree, often of precordial oppression and smothering, and usually of extreme anxiety on the part of the patient. Objectively the patient appears pale and gray, sometimes mildly cyanotic, with

increased perspiration. The pulse is regular, small, and extremely rapid, 180 to 220 beats per minute; auscultation reveals a rapid regular tachycardia with an occasional faint systolic murmur. The heart rate is not influenced by breathing, posture, or exercise, but may often be controlled by vagal or orbital pressure.

Diagnosis.—The diagnosis is made from the history of the attack, the physical findings during the paroxysm, and the electrocardiogram. Auricular paroxysmal tachycardia is of greater frequency than the others and is more benign.

The electrocardiogram reveals the tachycardia with minor changes in the various complexes which depend on the site of the cause of the paroxysm. Figure 16 shows the curves during and following an attack—the tachycardia in this case arising probably from the A-V node.

Prognosis.—The prognosis is for the most part good, although cases have been recorded where failure to check the tachycardia for a number of days or weeks has resulted in cardiac exhaustion and death. Sale reports a fatal case following extraction of a tooth. It is occasionally found with fibrosis of the myocardium.

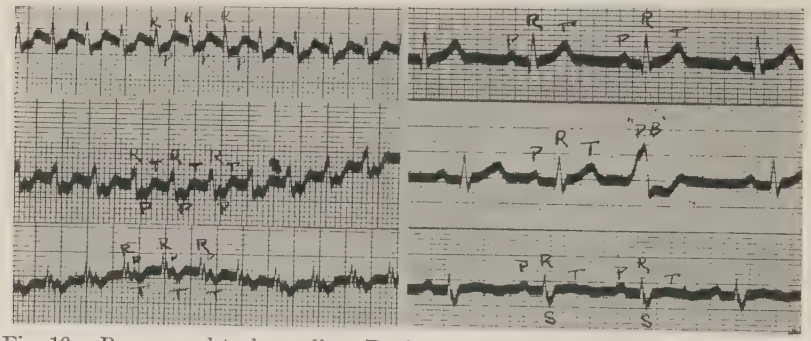

Fig. 16.—Paroxysmal tachycardia. During and following an attack. Probably nodal in origin—as evidenced by anomalous "P" wave interposed between "R" and "T." Right ventricular extrasystole "P. B." may be seen with sinus rhythm. Rate during paroxysm, 214. Rate after cessation of paroxysm, 68.

Treatment consists of attempts to bring the paroxysm to a close by means of digital pressure over the right or left vagus, orbital pressure, changes in posture, swallowing of various boluses or hard crusts of bread, morphin, digitalis, etc. *Quinidin* is said to be useful both for immediate treatment and as a prophylactic. Digitalis may be indicated.

V. **Auricular Fibrillation** (*Delirium Cordis, Pulsus Irregularis Perpetuus, Mitral Pulse*).—Auricular fibrillation is a condition of gross irregularity of the pulse, permanent or transitory, not necessarily associated with advanced myocardial disease, and due to complete absence of normal auricular systole. In place of normal contractions, the wall of the auricle undergoes a series of small rapid fibrillary contractions to which the ventricle responds in a markedly irregular fashion.

Incidence.—This type of irregularity is extremely frequent. It is said to be the commonest persistent arhythmia of the human heart. At least 50 per cent. of all such irregularities are cases of fibrillation, while 60 to 70 per cent. of all cases of heart failure entering general hospitals are of this type (Lewis).

Morbid Physiology.—Experimentally the auricle of dogs may be thrown into fibrillation by stimulation with the high-frequency current. Formerly fibrillation was thought to be due to impulses arising from a single irritable focus in the auricle. At present, largely because of the work of Mines, Garrey, and Lewis and his associates, it is believed to be due to a self-perpetuating ring of excitation in the auricle, the so-called *circus movement.* This abnormal ring of excitation is believed to originate about the mouth of the superior vena cava in the right auricle.

Only a relatively small number of the fine fibrillary contractions of the auricle caused by this circus contraction wave are responded to by the ventricle, the majority being lost or blocked by the junctional tissues. The rate of the ventricle in fibrillation is, therefore, an expression of the degree of blocking of the auricular beats. Under certain exceptional conditions, such as mild digitalis poisoning or disease of the bundle, the block may be complete. The ventricle then assumes the rhythm of its own pace-maker, that is, idioventricular rhythm.

Etiology.—Auricular fibrillation may be divided according to etiology: (1) into the rheumatic; (2) the non-rheumatic; and (3) the paroxysmal or transient type. Approximately 66 per cent. of all cases are *rheumatic.* This type attacks women between fifteen and forty years of age and those suffering from mitral stenosis. In such cases the onset of fibrillation often ushers in the period of acute failure of the heart muscle, and may be considered the last stage in the life-cycle of rheumatic mitral stenosis.

The *non-rheumatic* type occurs most frequently in men between forty-five and seventy years of age, in patients suffering from chronic cardio-vascular-renal conditions, generalized arteriosclerosis, and senile heart. While this type of fibrillation is probably the result of structural myocardial disease (chronic myocarditis, myocardial degeneration, or fibrosis), the heart often adapts itself remarkably well to the abnormal mechanism and patients may carry on the routine of their daily lives with surprisingly little inconvenience. Hyperthyroidism, goiter, and other toxic disturbances of the thyroid gland are not infrequently the etiological agents in this group of older patients with auricular fibrillation.

The third type of fibrillation, the *paroxysmal* or *transient,* has caused much interest in recent years because of the increasing frequency with which it is recognized.

Clinically, transient auricular fibrillation may be divided into the following groups:

1. That occurring during the course of acute infectious disease, such as pneumonia, acute rheumatic fever, typhoid, paratyphoid, diphtheria, influenza, etc.

2. That accompanying surgical anesthesia or appearing shortly thereafter.

3. Fibrillation brought on by toxic amounts of digitalis and associated with other signs of digitalis poisoning.

4. The so-called paroxysmal fibrillation of unknown origin seen more frequently in older men or women with hypertension, and associated with paroxysmal dyspnea, vertigo, and nausea.

5. That occurring paroxysmally under great emotional stress in nervous, phobic individuals, often in those addicted to immoderate use of tobacco, and in patients with exophthalmic goiter.

Symptoms.—The symptoms of auricular fibrillation vary from complete absence of subjective knowledge of the disorder to great anxiety and complaints of fluttering, breathlessness, precordial pain, pallor, cyanosis, and collapse. The pulse may be slow and nearly regular; rapid and extremely irregular both in time and force; moderately rapid and entirely regular (Dock and Levine and Hamburger); or exceedingly slow and entirely regular because of complete block (Fig. 17). Exercise usually increases the irregularity as the rate increases. This is in contrast to the decrease in irregularity after exercise in premature systoles. The rate as counted at the wrist is often less than at the apex (pulse deficit), both because of the failure of the very weak ventricular systoles to open the semilunar valves and because of the abortive ventricular contractions, too faint to initiate in the aorta a pulse wave that will reach the radial artery. Similarly, individual pulse beats at the wrist vary both in time and force, the latter variation showing clearly in the marked difference in systolic blood-pressure of individual beats.

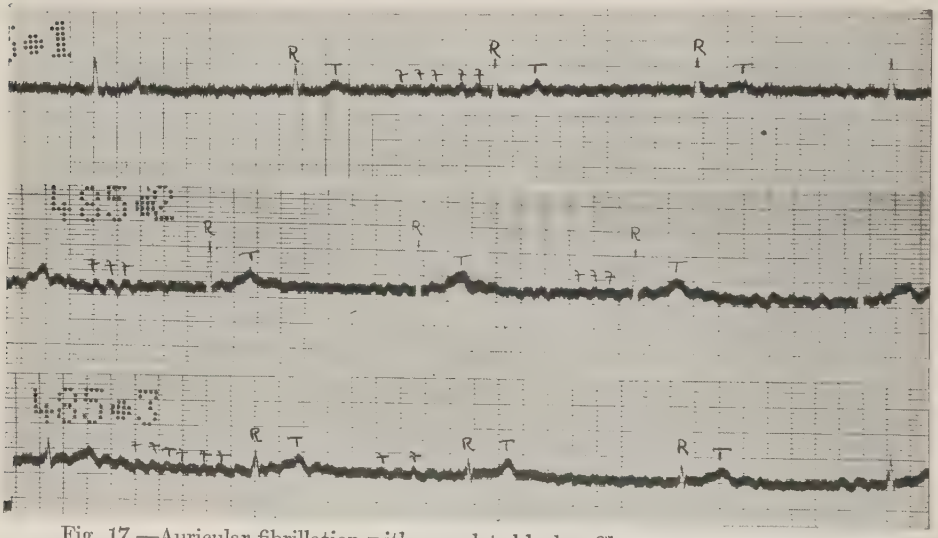

Fig. 17.—Auricular fibrillation with complete block. Slow regular ventricular systoles ("R-T") independent of rapid fibrillary waves of the auricle, evidence of complete "A-V" dissociation. Auricular rate, 420 (approx.). Ventricular rate, 33.

In the *paroxysmal cases*, the onset of fibrillation is often ushered in with sudden pain, collapse, or dyspnea. The sudden change from a slow regular rhythm to an extremely rapid and totally irregular one (*delirium cordis*) is striking and easily recognized.

Diagnosis.—The diagnosis of auricular fibrillation is made from observations of a grossly irregular pulse; the pulse deficit; the increase in arhythmia with increase in pulse rate; the frequently associated heart failure; mitral stenosis; cardiovascular disease; hyperthyroidism; etc. The presystolic murmur of mitral stenosis with a sinus rhythm becomes a protodiastolic or middiastolic rumble with the onset of fibrillation, due to the failure of auricular systole, the supposed cause of the presystolic murmur. In borderline cases the polygram and electrocardiogram are crucial. Electrocardiographic diagnosis rests on the absence of normal *P-waves*, the

presence of fine fibrillary waves (fff), the irregular response of the ventricle (*R-wave*) (Figs. 18 and 19). Clinically, differentiation between fre-

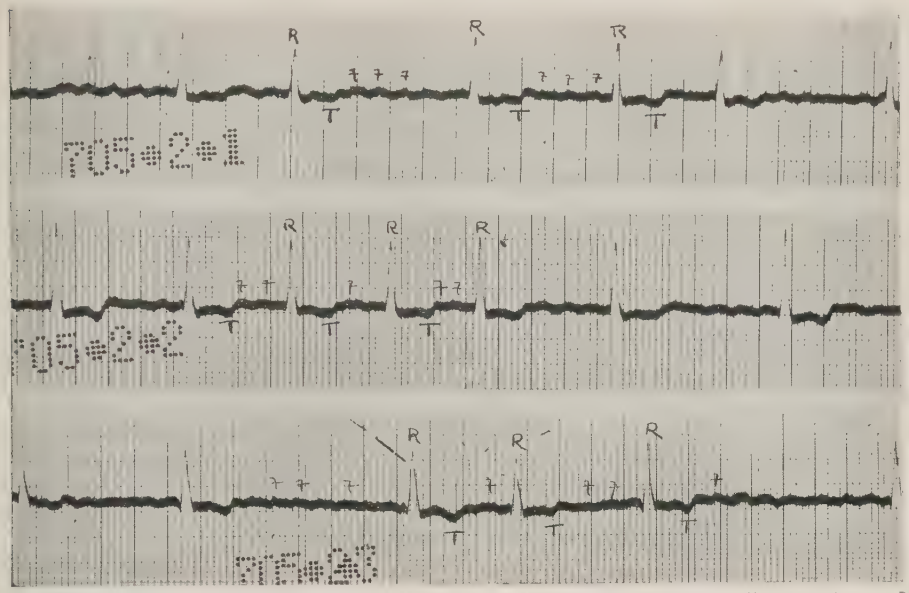

Fig. 18.—Auricular fibrillation. (Slow type.) Note the absence of "P" waves (normal auricular systole); presence of small "f" waves (fibrillation of auricle); slow irregularly placed "R" waves (slow irregular ventricular response). Auricular rate, 370 (approx.). Ventricular rate, 60 (average).

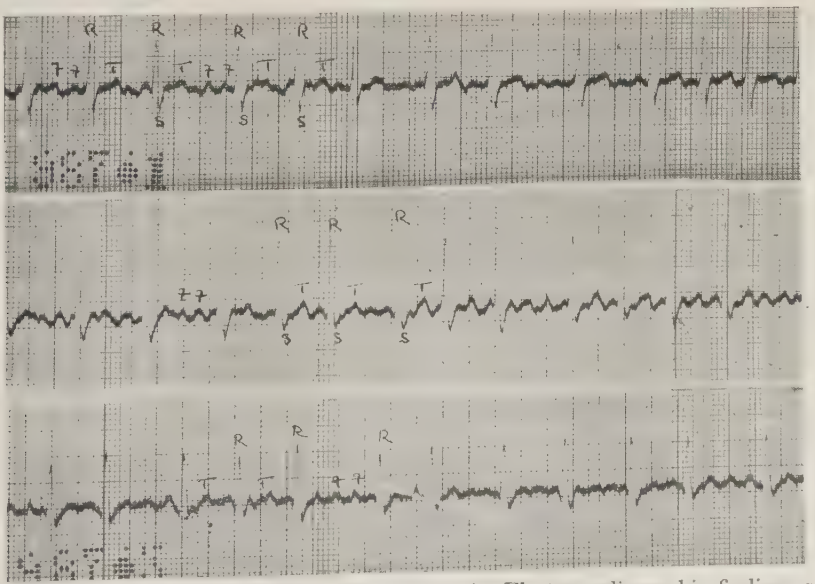

Fig. 19.—Auricular fibrillation. (Rapid type.) Electrocardiographic findings same as in Fig. 18, except more rapid rate of the ventricle due to more frequent response to supraventricular impulses from the auricle. Auricular rate, 420 (approx.). Ventricular rate, 150 (average).

quently recurring extrasystoles may be difficult. Here the variations in response to exercise and the electrocardiogram are determining factors.

Not infrequently *complicating* arhythmias exist—for example, complete or partial bundle branch block, premature ventricular systoles, etc. Their presence is evidence of a more wide-spread pathological process.

Prognosis.—While persistent auricular fibrillation is not of itself prejudicial to a relatively long active existence, there is no doubt that the functional efficiency of the heart is handicapped by it. Feil and Katz have presented evidence of the dynamic importance of auricular systole in men, and Barringer claims that auricular fibrillation exerts a deleterious influence on cardiac efficiency. Willius, from a study of 500 cases, concludes that "the mortality attending auricular fibrillation doubles and in some groups trebles that occurring in similar types of heart disease not complicated by this type of arhythmia."

Treatment.—In patients with auricular fibrillation of the rapid type with moderate or advanced heart failure *digitalis* is of positive and striking value. It is employed in these cases for two purposes: first, to improve the efficiency of the heart and circulation itself; and second, to retard the ventricular response to the rapidly beating auricle to approximately 70 or 80 beats per minute. In hearts with any measurable degree of muscular integrity such results are possible. In the adult, 15 to 30 minims of a potent tincture of digitalis three or four times a day is usually sufficient to accomplish this. The permanent reduction of the ventricular rate to 80 beats per minute or less may follow without further administration of digitalis, but it may be necessary to take between 5 and 10 minims three times daily for months or even years to accomplish this end.

In recent years a successful attempt to re-establish a sinus rhythm in auricular fibrillation by the administration of *quinidin sulphate* has been made. Lewis and his associates have recently defined its action in fibrillation as an ability to lengthen the refractory period of muscle, thus bringing the bizarre circus movement responsible for fibrillation to a standstill and permitting the normal pace-maker to resume dominance over the heart's rhythm.

In the transition between fibrillation and sinus rhythm, auricular flutter with transitory increase in ventricular rate, tachycardia, and palpitation may occur. Quinidin sulphate may be given in 3 to 6 grain (0.2–0.4 gm.) capsules, three times a day before meals, later every two hours by mouth, following a preliminary trial for quinin idiosyncrasy. Preliminary digitalization in the presence of moderate heart failure or rapid pulse is now generally practiced, in order to avoid such occasional untoward results as the embolic phenomena, increase in failure, and even death which have been observed.

Hamburger and Priest administered quinidin to 18 patients suffering from auricular fibrillation. In 11 cases (61 per cent.) a normal cardiac mechanism was re-established, which in 5 cases (27 per cent.) has persisted three months or more. One patient has maintained a sinus rhythm uninterruptedly for eleven months.

Cases of acute fibrillation or recurrent paroxysmal fibrillation are most amenable to quinidin treatment, and the duration and frequency of paroxysms can be promptly controlled without undue risk. When heart failure is moderate or advanced, and there is history or evidence of embolism, endocarditis, heart-block, angina pectoris, coronary disease, quinin idiosyncrasy, or prolonged chronic fibrillation, quinidin should not be given.

VI. Auricular flutter is an abnormal cardiac rhythm in which rapid, regular, small auricular contractions replace the normal auricular systole, the ventricle in most cases responding regularly to every second, third, or fourth auricular beat.

Occurrence.—It is closely allied to auricular fibrillation, but is much less frequent. Hamburger states that during a period of three years auricular flutter occurred among his patients 10 times; fibrillation 120 times. Blackford and Willius believe the proportion of 16 : 63 fair.

Morbid Physiology.—Lewis and his associates have recently shown that the contraction wave of flutter follows a "circular and never-ending path in the auricle, the circuit being completed at a rate of 240 to 350 per minute in different subjects." The mechanism is then similar to the circus movement of fibrillation, except that in the latter the circuit is smaller in diameter and follows a much more sinuous course. As in fibrillation, partial A-V block is practically always present, the ventricle responding regularly to every second, third, or fourth auricular beat. Sometimes when the ventricular rate is irregular the ventricle responds intermittently to every second, third, fourth, or even fifth beat of the auricle. Occasionally for a short period the ventricle may respond to *every* beat of the auricle, and thus cause a severe tachycardia with a heart rate of as much as 350 beats per minute accompanied by syncope and collapse. The degree of block then becomes the basis for the ventricular rate. The pulse may vary from 32 beats per minute when there is complete block and an idioventricular rhythm to the full rate of 320 per minute (Blackford and Willius). However, in general clinical experience flutter is most frequently seen as a 2 to 1 block with a ventricular rate between 120 and 175.

Etiology.—The etiology of auricular flutter is in no way specific. *Syphilis* and *rheumatism* seem to play a minor rôle. *Tonsillitis, grippe,* and *acute respiratory infections* have frequently been associated with the condition. Blackford and Willius found *exophthalmic goiter* in 4 cases. Flutter is said to be more frequent between the fortieth and sixtieth year, although it has occurred in a child of four months (Lewis) and in a man of eighty-two.

Symptoms.—Flutter is seen more frequently in adult or middle-aged men than in women, occurring often as short attacks of tachycardia simulating simple paroxysmal tachycardia. It is apt to make its appearance in atherosclerotic individuals with degenerative myocardial lesions and during early or advanced heart failure. In such patients complaints of palpitation, weakness, periodic dyspnea, faintness, flatulence, pallor, and polyuria are not uncommon. Physical examination reveals the "tick-tack rhythm," and usually the signs of advanced cardiac failure.

Diagnosis.—Fine gradations between flutter and fibrillation are frequently seen, the so-called *impure flutter* or mixed flutter and fibrillation. In a given case the distinction between impure flutter and fibrillation may be extremely difficult, if not wholly impossible. Frequent alternation of flutter and fibrillation at different times in the same patient is not uncommon. The electrocardiogram in flutter is in most cases typical; the frequent fine regular *P-waves*, with usually equally spaced ventricular complexes, are easy to distinguish from the bizarre, markedly irregular, fine "*f*"-waves of fibrillation on one hand and the more prominent *P-waves* of sinus rhythm on the other (Fig. 20). During periods of extreme tachy-

cardia the differentiation from paroxysmal auricular tachycardia may be difficult electrocardiographically as well as clinically.

Prognosis.—The prognosis in flutter depends on the degree of heart muscle involvement, the response to treatment, and the extent of cardiac reserve as measured by careful history and physical findings. Lewis cites a patient in whom flutter persisted uninterruptedly for seven years, the heart beating without cessation at 140 per minute. Hamburger has seen one case of paroxysmal flutter in a young man without signs of heart failure, which was easily controlled by vagal pressure and quinidin.

Treatment.—Many authors emphasize the value of *digitalis* in full amounts: first to increase the A-V block, thus decreasing the ventricular response and slowing the pulse, and later in sufficient dosage to convert flutter into fibrillation. If the drug is then withdrawn fibrillation is said to cease and sinus rhythm to be re-established. Hamburger's experience

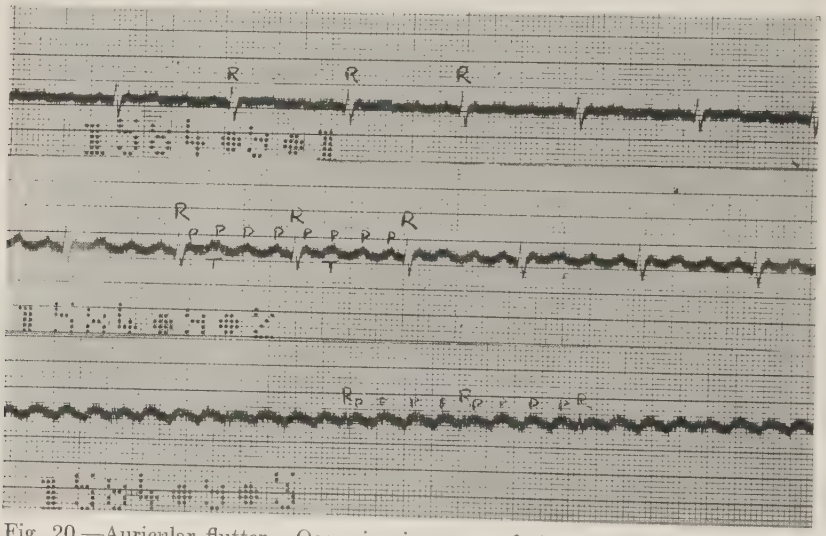

Fig. 20.—Auricular flutter. Occurring in a man of sixty-five years with a perfectly regular slow radial pulse with heart failure-flutter totally unsuspected—found in routine electrocardiograph examination. Auricular rate, 272. Ventricular, 68. 4–1 "A-V" block.

with this method has not been so successful. While fibrillation is not hard to produce with digitalis there is usually reversion to flutter upon its discontinuance. Blackford and Willius found that by giving digitalis until there was complete block, permanent sinus rhythm was more frequently obtained. Wedd suggests combining *quinidin* with digitalis to break up the circus rhythm by raising the refractory period of heart muscle. *Vagal pressure* has been shown capable of converting experimental flutter into fibrillation; in clinical flutter it may also temporarily slow the ventricular rate by increasing the A-V block, while the auricular rate continues unchanged.

Disturbances of Impulse Conduction

VII. **Heart-block.**—Delay or interference (block) of conduction of the excitation wave of the heart may result from mechanical interference (experimental ligation, compression, cutting the His-Tawara system);

from acute infections (influenza, pneumonia, diphtheria, acute streptococcus infections, acute rheumatic fever); from vascular impairment (embolism); from vagal stimulation; from chronic disease processes (myocardial degeneration and fibrosis, gumma, atherosclerosis); from various drugs (digitalis, adrenalin, strophanthus, aconitin, muscarin, physostigmin, nicotin, morphin, potassium salts); and from various toxic agents (fever, asphyxia, anoxemia, glyoxylic acid, diphtheria toxin).

The location of the block may be in a variety of places: (1) in the pathway between the sino-auricular node and the auricle; (2) between the auricle and the ventricle, in the A-V node or bundle of His; (3) in the bundle branches; and (4) in the arborizations of the Purkinje system.

(*a*) Sino-auricular block was first described by Mackenzie in 1902 as an accompaniment of influenza. Later, cases were described by Wenckebach in 1906 in otherwise normal individuals, by Hewlett in 1907, and by Rich in 1908 in advanced cardiac and arterial disease. Sino-auricular block is a condition in which both auricular and ventricular complexes

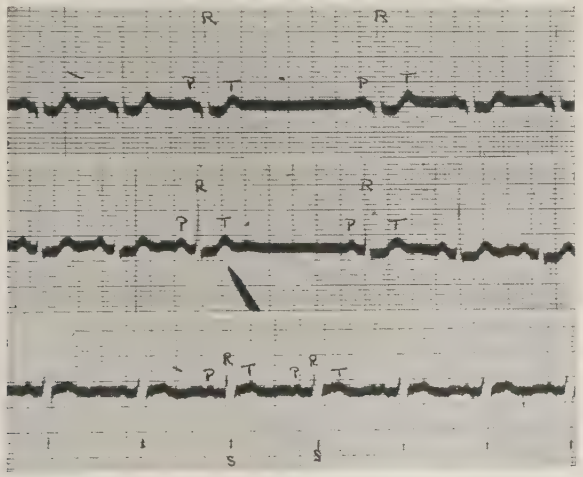

Fig. 21.—Sino-auricular block. Abrupt standstill of both auricular and ventricular systoles in Leads 1 and 2 for a period equal to more than two normal cycles. Left ventricular preponderance (high R, deep S) is also present.

drop out completely, and a regular rhythm is interrupted by a long cycle. It may often be abolished by atropin, deep breathing, swallowing, or exercise, and increased by vagal pressure. Levine calls attention to the frequency of sino-auricular block after taking digitalis, and Eyster and Evans have observed its association with nodal rhythm. In general, the sino-auricular block is probably due to abnormal vagus tone and is of little or no importance clinically. The electrocardiogram shows a complete disappearance of auricular and ventricular systole (Fig. 21).

(*b*) Auriculoventricular block or dissociation is usually termed, in popular speech, "heart-block." It may be manifested by: (1) a delayed A-V conduction time with increased *P-R* interval (Fig. 22); (2) occasional dropped beats; (3) regular dropped beats with a regular ratio 10 : 9, 8 : 7, 6 : 5, etc.; (4) regular ventricular response to every second, third, or fourth auricular beat; 2 : 1, 3 : 1, 4 : 1 (Fig. 23) rhythm; (5) complete A-V block, with idioventricular rhythm.

History.—Morgagni in 1761 recorded the first case of heart-block (Osler), while the Irish physicians, Robert Adams in 1826 and Williams Stokes in 1846, published clinical accounts of the disease, later to be known as the Adams-Stokes' syndrome. Gaskell in 1881 introduced the term "heart-block," while in 1893 His discovered and described the narrow band of neuromuscular tissue between the auricles and ventricles—the auriculo-ventricular bundle.

Etiology.—Clinically the lesser grades of partial A-V block are probably seen most frequently during active *digitalis administration*, particularly in

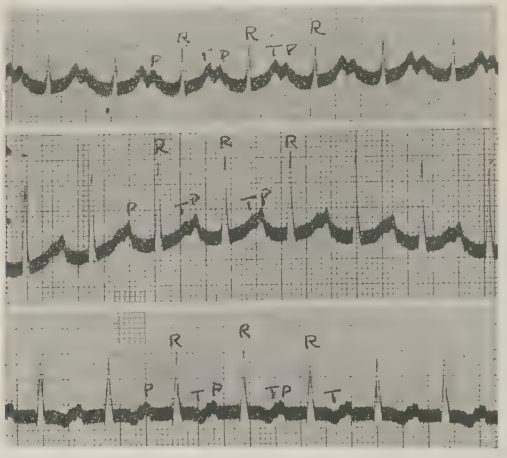

Fig. 22.—Beginning heart-block. Showing delay in A-V conduction time. Prolonged P-R interval to 0.28 sec. (normal 0.11–0.16 sec.).

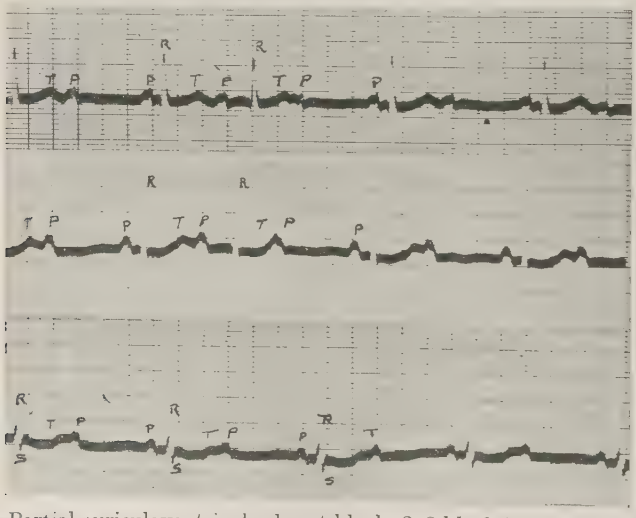

Fig. 23.—Partial auriculoventricular heart-block; 3–2 block in Leads 1 and 2: one 2–1 block in Lead 3. Note the progressive lengthening (delayed conduction) in P-R interval until ventricle ceases to respond.

patients with *fever* and in individuals suffering from such *acute infections* as acute rheumatic fever, acute broncho- and lobar pneumonia, influenza, and diphtheria. While digitalis in such cases often brings out a latent block, disturbed conduction of this type is also seen with great frequency in these infections without digitalis. The most complete transitory block

ever observed by Hamburger was in a young boy during an acute hemolytic streptococcus tonsillitis (Fig. 24).

Complete chronic block is usually seen in older atherosclerotic individuals, and is often based on syphilis with fibrous myocarditis, fibrillation, or flutter. Twelve cases of *congenital block* caused by defective development of the A-V bundle have been reported. *Increased pressure* within the sheath surrounding the conducting bundle, as well as pressure from tumors, aneurysms, etc., may cause block.

Incidence.—In the writer's 1200 cases, block of all types ranked third in frequency of the irregularities, 9.6 per cent., in contrast with 11.2 per cent. for premature systoles, and 10 per cent. for fibrillation. The types of block were as follows: partial A-V block 3.1 per cent.; bundle branch block 2.8 per cent.: delayed *P-R* interval 2.5 per cent.; complete A-V block 0.8 per cent.; sino-auricular block 0.4 per cent.

Morbid Anatomy and Physiology.—The histological changes observed after death from heart-block (Adams-Stokes' syndrome) are: (1) gum-

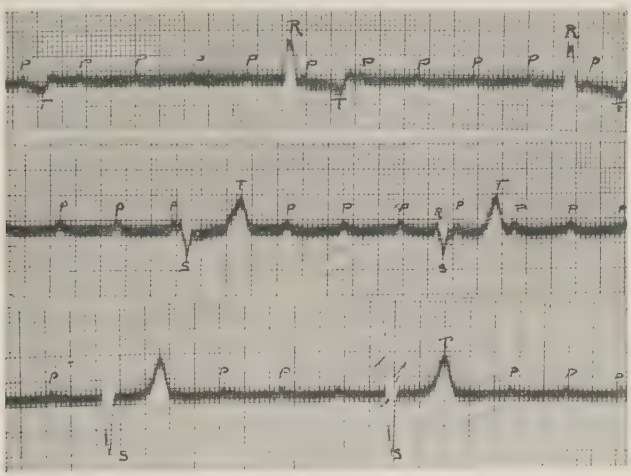

Fig. 24.—Complete auriculoventricular dissociation. Occurring in a young boy with acute streptococcic tonsillitis. Note independent auricular and ventricular systole (idioventricular rhythm). Auricular rate, 136. Ventricular rate, 28.

matous changes; (2) calcium deposits with atherosclerosis; (3) myomalacia; (4) inflammatory changes caused by progression of endocardial ulceration to the A-V system by embolic abscess formation in septum, or from rheumatic nodules; and (5) the lesions of diphtheria, tuberculosis, and adiposity of the A-V system.

Although it has been firmly established that lesions of the conductive system may cause partial or complete heart-block they may exist (even though of considerable extent) without block, and furthermore partial or complete block may exist without lesions of the bundle.

It is common knowledge that varying degrees of block frequently result from massive digitalis therapy, from vagus pressure (extracardial block), and from acute infections. Hamburger states that such partial or complete blocks occur especially during acute respiratory infections with and without digitalis therapy. From many sources it is now becoming clear that purely functional disturbances arising from stimulation of extra-

cardial nerves and from digitalis become much more severe when anatomical changes in the A-V system already exist. Wenckebach believes that when there is a striking reaction to vagal pressure (production of idioventricular rhythm) there is much likelihood of an anatomical lesion of the heart muscle.

Symptoms.—Partial block may be unassociated with subjective symptoms, or the patient may complain of weakness, palpitation, dyspnea, faintness, and giddiness. The pulse may be slow and regular, with an occasional dropped beat, or it may be regularly coupled or trebled—*pulsus bigeminus, trigeminus,* etc.

In 1827 Adams of Dublin reported the case of an officer, sixty-eight years old, whose pulse was about 30 and who, during the last seven years of his life, had 20 attacks of brief unconsciousness attended by stertorous breathing and increasing bradycardia. He died during an attack. The *Adams-Stokes' syndrome* may vary from slight giddiness or faintness to complete unconsciousness with twitching of face muscles and generalized convulsions. Mackenzie noted thirty attacks of unconsciousness in one hour, which occurred when the ventricles stood still for ten seconds. Convulsions developed when the ventricles stopped for sixteen seconds.

Prognosis.—Patients with mild forms of heart-block, even when the pulse rate is about 30, may lead quiet uneventful lives for ten or twenty years. With complete block associated with recurrent syncopal attacks the patient's life is uncertain, and death usually occurs during one of the attacks. The patient is often found dead in bed or elsewhere (Mackenzie). In milder cases, no grave conditions arise from the delay or partial block itself, but its recognition should be a warning that myocardial changes are present.

Treatment.—If the block is incident to digitalis administration discontinuance of the drug will result in cure. Acute heart-block due to infection usually subsides with passing of the infection. If syphilis or arteriosclerosis is a factor, antiluetic medication, particularly *potassium iodid,* may be useful. If heart failure exists, *digitalis* should always be given, particularly when there is complete block and the ventricle is already isolated and under control of its own independent pace-maker (idioventricular rhythm). If the block seems influenced markedly by vagus pressure, *atropin* may be given to relieve or modify the effect of the vagus.

In complete block, *adrenalin* has recently been used as a stimulant for the sympathetic end-apparatus in the ventricle in an attempt to increase the ventricular rate. DeGraff and Weiss find that subcutaneous doses of 1 to 2 mgm. increase the ventricular rate considerably, the increase lasting for fifteen minutes to several hours. Atropin also increases the ventricular rate slightly by removal of the inhibitory influence of the vagus. If adrenalin is given after paralysis of the vagus by atropin there is an increase in both the auricular and ventricular rate. Recently Levine and Cohn have described the beneficial effects of barium chlorid on Adams-Stokes' disease.

(*c*) Bundle Branch Block.—Complete or partial interference with conduction of the excitation wave may occur in either or both branches of the bundle of His (bundle branch block). The electrocardiographic evidence of such interference is now thought to consist of the following three facts: (1) widening (delay) in the *QRS* complexes; (2) notching or splintering of the *QRS* complexes; (3) presence of a diphasic ventricular curve with

T in the opposite direction to *R*. Block of the right branch has the general appearance of a left preponderance; block of the left branch, the reverse.

(*d*) Arborization Block (*Intraventricular Block*).—Arborization block implies interference with conduction through the fine terminal divisions of the Purkinje system (subendocardial fibers). Electrocardiograms of such abnormalities are said to differ from bundle branch block in that the *diphasic curve* is absent, while a negative *T-wave* and a splintered *R-wave of low amplitude* are characteristically present.

The main clinical interest of both bundle branch block and arborization block at present is the *prognosis*. Oppenheimer and Rothschild and others believe that the demonstration of this type of block is of ominous prognostic significance, a high percentage of their patients dying within two years after signs of bundle branch block had appeared.

VIII. **Alternation of the heart beat** (*pulsus alternans*) is the term applied to alternating strong and weak contraction of the muscular walls of a heart chamber or of a strip of cardiac muscle (Lewis).

The condition is best recognized clinically by alternating strong and weak radial pulse beats. The sphygmomanometer is helpful in differentiating the alternating beats (Herrick). Alternating variations in *R*- and *T-wave* may sometimes be recognized in the electrocardiogram, but polygraphic tracings show the alternate variations more constantly. The exact cause and mechanism of *pulsus alternans* is unknown, although a variety of theories and hypotheses have been advanced by various authors. It is generally agreed that this condition is an evidence of profound and wide-spread deterioration of the heart muscle, or of severe strain upon the heart. It often develops in the senile heart associated with paroxysmal tachycardia or auricular flutter. It is not infrequently associated with angina pectoris, and may occur occasionally with digitalis poisoning or in acute infections (pneumonia). It may be simulated by *pulsus bigeminus* or by recurrent extrasystoles, the latter often serving to disclose latent disturbances. Alternation, once present, is usually permanent, although variations in the degree of alternation may occur. Auscultation may reveal no changes in the apical tones, or may show concordant or discordant variations synchronous with alternations of the pulse.

Walter W. Hamburger.

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DISEASES OF THE MYOCARDIUM

The diseases of the myocardium are almost invariably secondary to local or general disease of other organs or tissues. Those of chief clinical importance are either inflammatory or degenerative processes. The primary condition is usually an infection, intoxication, or nutritional disturbance, which may be more or less restricted to the heart as in coronary disease, or, generalized. When the primary disease causes well-defined local or constitutional symptoms, or symptoms referable chiefly to organs or tissues other than the heart, involvement of the heart muscle is usually regarded as a complication: if, however, the myocardial damage first becomes evident after subsidence of the symptoms of the primary disease, it may be regarded as a sequel. A condition is usually considered myocardial disease when the cardiac symptoms dominate the syndrome. Generally speaking, therefore, myocardial diseases should not be regarded as

entities, etiologically, pathologically, or clinically, but it is, nevertheless, customary and convenient to discuss them as more or less distinct syndromes. The names of the several types of myocardial disease are often employed in diagnosis, a fact which is to be deprecated unless the name be qualified by mention of the probable etiology. When the cause cannot be determined that fact should be stated in the diagnosis.

Inflammatory, degenerative, and reparative changes may often all be present in the same heart at autopsy, and it is frequently difficult or impossible to decide which is primary. During life it is much more difficult to make a diagnosis of the probable anatomical changes present in the heart, especially since there are no symptoms or physical signs peculiar to the different pathological processes. In other words, *the changes in the heart muscle itself all produce a more or less common syndrome.*

Hypertrophy and dilatation, which are two of the most constant and characteristic evidences of the myocardial diseases, are often separately described. Inasmuch as they are almost invariably secondary to the myopathies or to various mechanical factors, such as valvular lesions, long-continued hypertension, etc., this seems unwise. They will, therefore, be mentioned in their appropriate places as physical signs or symptoms.

A form of hypertrophy which occurs in the absence of such mechanical causes as high blood-pressure or valvular disease is often described as "idiopathic" hypertrophy. With increasing knowledge of the etiological factors of hypertrophy this term is rapidly falling into disuse. It should be abandoned entirely. The practice of classifying ventricular hypertrophy as *concentric*, *simple*, and *eccentric* is also very properly being dropped. "Concentric" hypertrophy was described as that form in which the ventricular walls were more or less increased in thickness while the size of the cavity was actually smaller than normal. It is now certain that this contraction of the ventricular cavity is entirely a postmortem phenomenon. "Simple" hypertrophy is merely hypertrophy without evident dilatation, while "eccentric" hypertrophy is a form in which dilatation is an accompanying feature. Modern usage merely describes these disturbances as hypertrophy, dilatation, or hypertrophy with dilatation.

The mechanisms which evoke hypertrophy and dilatation have long been the subject of controversy. The modern researches of Wiggers and others have done much to clarify many of the problems. The following brief review is based largely on the work of Wiggers.

Dilatation.—When the normal ventricle is made to eject blood against a greater resistance than that to which it is accustomed, or when the contractile power of the ventricle is impaired, while the resistance remains normal, strain of the heart sets in. Under such conditions the ventricle tends to reduce its systolic discharge; the blood which consequently remains in it when added to that which enters during diastole, increases the diastolic volume and raises the initial tension to which the muscle is subjected. It is a cardiac law that increased lengthening and stretching increase the irritability and contraction so that the systolic output is restored to normal or above normal. This capacity for adaptation is limited, and when the elastic resistance and tonic contraction of the muscle can no longer meet the increased strain, the heart fails and dilatation of the ventricle ensues. In cardiac failure the heart is no longer able to discharge as much blood as it receives. Dilatation may result then from two causes: passive dis-

tention, when the elastic resistance of the myocardium is overcome by increased initial intraventricular pressure; and diminution of tonus, which allows the ventricle to accommodate an increased volume of fluid without raising the initial tension necessary to increase the strength of its beat.

Hypertrophy of the heart involves an increase in both the size of the individual muscle cells and the number of the muscle fibrils. The precise nature of the stimulus which evokes cellular hypertrophy is not known. In the vast majority of instances, however, the process is related directly to the stretching of the muscle fibers by increased ventricular filling, or by ventricular dilatation. Krehl suggests that inflammatory processes may act as irritants and cause hypertrophy; and Albrecht describes a condition which he calls "myocarditis progressiva," in which he believes that the hypertrophy is part of the inflammatory reaction. These processes, however, are so constantly associated with the functional changes which increase the length of the ventricular muscle fibers in diastole that it is impossible to prove that they are the immediate and direct causes of hypertrophy. In the present state of our knowledge it is best to regard them as secondary, and to believe that hypertrophy depends primarily on continued muscle stretching and increased work.

Acute Myocarditis.—Definition.—Acute myocarditis is an acute inflammation of the walls of the heart.

Incidence.—The disease occurs at all ages and in both sexes. It is most common in childhood and early adult life, and is comparatively rare in individuals over forty. The frequency with which acute myocarditis occurs cannot be stated, because it often runs its course without producing any symptoms which make diagnosis possible. The diagnosis is also often made when no myocardial lesions are found at autopsy.

Etiology.—Acute myocarditis is probably always secondary. It may be caused by any of the acute infections, and occurs most frequently in acute rheumatic fever, diphtheria, influenza, typhoid fever, scarlet fever, smallpox, erysipelas, septicemia, pyemia, and malaria. In toxic adenoma of the thyroid and Graves' disease acute myocardial degeneration is sometimes very extensive, especially in the rapidly fatal cases. It may result from direct invasion of the heart by the infecting organisms, or from the action of their toxins which reach the heart through the blood-stream. Ulcerative endocarditis is a rare cause. When acute myocarditis appears to be the only discoverable disease it is often called *idiopathic*, but as it is probably secondary, even in these cases, the term "*cryptogenic*" is more suitable.

Morbid Anatomy.—The most common lesion is diffuse parenchymatous degeneration. Grossly, this appears as cloudy swelling of the muscle and microscopically, as a granular change in the sarcoplasm of the muscle cells, which may more or less obscure the striations. This lesion is usually due to the action of bacterial or other toxins. It may undergo complete resolution.

Less frequently the muscle cells, interstitial tissues, and blood-vessels are all involved in an inflammatory process. Between the muscle fibers there may be infiltration of round cells, leukocytes, and an albuminous exudate. The muscle fibers undergo albuminous degeneration and lose their markings, or show evidence of hyalin or fatty degeneration. Infiltrations of round cells frequently occur beneath the pericardium and the

mural endocardium, so that these membranes are involved with the myocardium and the condition becomes pathologically carditis rather than pure myocarditis. The destroyed muscle cells may be absorbed gradually and replaced by fibrous scar tissue. This is seldom visible to the naked eye, but occasionally the scars are quite large and even lead to bulging of the wall with the formation of small cardiac aneurysms. The inflammatory process is generally rather diffuse, but may be patchy in its distribution. As a rule, the ventricles are chiefly involved and the muscle is friable and grayish or yellowish and cloudy in appearance.

In some cases the chief or only lesion is an acute interstitial productive myocarditis. This manifests itself as a primary increase in the cells of the fixed connective tissue and adventitia of the vessels with invasion of lymphocytes, plasma cells, and eosinophilic leukocytes. Healing results in the formation of multiple minute scars which are very difficult to discover.

A rare form of myocarditis occurs in sepsis and pyemia when bacterial emboli lodge in the finer arteries of the heart. This may produce one or many abscesses. A single large abscess may involve the entire thickness of the ventricular wall and may cause sudden death by rupture, or may heal and leave a thin wall of fibrous tissue which bulges and forms a cardiac aneurysm.

Rheumatic myocarditis produces peculiar lesions known as *Aschoff's nodules*. These are submiliary collections of large spindle-shaped or branching cells with large, sometimes multiple, nuclei. They probably arise from the connective tissue and are accompanied by collections of lymphocytes and eosinophilic leukocytes. They occur in the interstitial tissues, usually around the blood-vessels and just beneath the endocardium. The interventricular septum is frequently involved and invasion or destruction of portions of the conducting system often produces varying grades of heart-block. The nodules are seldom visible on gross examination, but are readily seen under the microscope. They occur only in rheumatic fever, but cannot always be demonstrated even in proved cases. An insignificant grade of parenchymatous and interstitial myocarditis occasionally accompanies the nodules.

Diphtheritic myocarditis is in most instances an acute, diffuse degeneration due to the action of the toxin. The muscle, the conducting system, and the nerve structures are especially involved. If the damage is not too extensive, the destroyed muscle cells are absorbed and replaced by scar tissue which is widely distributed and usually not grossly apparent.

Symptoms.—The onset of acute myocarditis can rarely be determined with accuracy because the condition usually develops during or immediately after an acute infection. There are no characteristic symptoms, but the condition is to be suspected if circulatory disturbances appear during or following acute infection. Even under such circumstances diagnosis can seldom be made with certainty. The symptoms of myocarditis may not develop for several weeks after subsidence of the acute infection.

Acute myocarditis often causes anxiety and a sense of oppression or pain in the chest, especially in the precordial region. The *heart action* is usually disturbed, the rate is rapid, and any of the forms of irregularity may appear. Bradycardia is an occasional manifestation. The pulse is soft, small, easily compressible, and reflects the irregularity of the heart.

The blood-pressure is usually diminished. The apex impulse is diffuse, displaced to the left, and may be feeble when palpated. The heart is usually dilated, and if this is marked the area of cardiac dulness is enlarged and systolic murmurs may be present at the base or apex, or over the whole heart. The sounds are often slapping, and the first sound is likely to be of poor quality.

When *heart failure* sets in the usual symptoms of passive venous congestion and deficient circulation develop. There are cyanosis, dyspnea, orthopnea, and cough; and the veins of the neck are full. There may be nausea and vomiting with a sense of fulness and pain in the epigastrium and right hypochondrium. Dependent edema begins to appear, and the urine becomes scanty and contains albumen, casts, and often an excess of urates. With these symptoms there are moist râles and impaired voice and breath sounds, with diminished resonance at the base of the lungs, or evidences of pleural effusion, especially on the right side. The liver may be considerably enlarged by congestion, its lower border may extend down to the umbilicus, and systolic pulsation may be palpable in it. There is marked tenderness in the hepatic region. Ascites may develop. These are all symptoms common to cardiac failure and are in no way peculiar to acute myocarditis, but when they occur during or shortly after an acute infection in a patient whose heart was previously normal the diagnosis of acute myocarditis can be made with reasonable assurance.

Fever is common, but is often masked by that due to the primary infection. It is usually moderate (seldom above 103° F.), and may be continuous or intermittent. Moderate leukocytosis may occur with or without a relative increase in the polynuclear cell count, but a normal count or even leukopenia is quite as frequent. There is usually moderate secondary anemia.

Rheumatic myocarditis occurs to some extent in probably not less than 90 per cent. of all patients with acute rheumatism. The myocardial changes, however, in the majority of cases are slight and often transitory, or heal without leaving clinical evidence of their existence. Such slight involvement usually passes unrecognized unless special search is made. In the more pronounced cases, the usual signs and symptoms are those just described. Impulse conduction is frequently delayed. This is recognizable only when graphic records are made, because the heart-block is seldom sufficient to cause dropped beats. Premature contractions are very common, and more serious arhythmias, such as auricular fibrillation, occasionally develop. Tachycardia is the rule, although bradycardia may be encountered as a rare and usually grave symptom. Rheumatic endocarditis and pericarditis very frequently accompany myocarditis and render its diagnosis extremely difficult in many cases.

Diphtheria is complicated with myocarditis fairly often, especially when the use of antitoxin has not been adequate or early. This form of myocarditis may be slight and cause few symptoms, but when diphtheria is neglected it is likely to be very severe and often rapidly fatal. Even in patients with few or no recognizable cardiac symptoms the heart may be so extensively damaged that moderate exertion may cause collapse or sudden death. The heart is dilated, the pulse is feeble and very readily compressible, and the patient is easily exhausted. A systolic murmur due to a relative mitral insufficiency is common, and the heart sounds are

of poor quality with frequent gallop rhythm. Tachycardia is the rule in the first few days, and sino-auricular block or premature contractions are frequent. Bradycardia is more likely to occur in this form of myocarditis than in any other and is of gravest significance, as it indicates extensive damage to the conducting system with consequent severe heart-block. This symptom develops suddenly during the convalescence from diphtheria, and is to be anticipated when tachycardia persists beyond the fourth or fifth day. It is almost invariably fatal within forty-eight hours.

Diagnosis is always difficult and sometimes impossible. In many cases it is little more than an inference based on the conditions under which the symptoms have developed. The diagnosis at best is usually one of probability only, and must often be reached mainly by a process of exclusion. Acute myocarditis is not infrequently seen after death in patients who have had no symptoms from which a diagnosis could be made during life.

Feeble, rapid pulse, low blood-pressure, weakness, exhaustion, digestive disturbances, restlessness, and anxiety are produced in acute infections by *circulatory failure of vasomotor origin* as well as by acute myocarditis. Differential diagnosis of their cause is often impossible. Dilatation of the left ventricle may cause relative insufficiency of the mitral valve. The signs of this type of insufficiency are the same as those evoked by mitral endocarditis. Inasmuch as endocarditis is a common accompaniment of acute myocarditis, especially in rheumatic fever, differentiation between the two forms of mitral incompetence is usually very difficult if, indeed, it is possible.

Course and Prognosis.—Acute myocarditis may be very mild and permit early and complete recovery, or so extremely severe that it is fatal within a few days. Death is most likely to ensue in the septic and diphtheritic types. The intensity of the clinical manifestations may not be a true index of the ultimate prognosis. Patients with few and slight symptoms may succumb rapidly, while others with marked clinical symptoms may gradually recover and suffer little permanent functional impairment of the heart. Partial recovery is common, the heart remaining permanently damaged to a considerable extent, or the myocarditis may become chronic. The physician should always, therefore, be guarded in giving a prognosis either as to probable duration or ultimate outcome.

Treatment should begin with efforts to prevent the development of acute myocarditis in every patient with one of the probable causative infections. The patient should be kept at complete rest in bed and should be forbidden to make any unnecessary effort which would throw added strain on the heart. This should be continued until all evidences of active infection have disappeared. Where the infection has been severe, or of long duration, rest in bed should continue well into convalescence. In acute rheumatic fever the patient should not be allowed to sit up in bed until the temperature has remained normal for at least two weeks, and when cardiac symptoms have been present this period should be much lengthened. The early and adequate administration of antitoxin is the most effective means of preventing the development of diphtheritic myocarditis. This should be combined with the measures just outlined.

The treatment of acute myocarditis itself consists primarily in securing *maximum rest for the heart*. During the active stage the patient must be confined to bed. The use of the bed-pan and urinal must be insisted on

and the subject should not even feed himself and must not sit up in bed. All forms of mental excitement must be avoided, and abundant sleep secured by the use of bromids and simple sedatives. *Drug therapy* is not called for unless there be evidence of cardiac failure. Cardiac stimulants may then become necessary. Strychnin and alcohol have their advocates, but there is no satisfactory evidence that they are of any real value. Digitalis, which is the most valuable agent in the treatment of chronic cardiac disease, is frequently of little or no value in acute myocarditis, and may be actually dangerous because it increases an existing heart-block. If tried, it should be administered in small doses (1 to 2 c.c., 15 to 30 minims of the tincture, three or four times daily) and a close watch maintained for unfavorable effects. Caffein is often a better stimulant in such conditions, and is best given subcutaneously in the form of one of the soluble preparations. Intramuscular injection of epinephrin (adrenalin) is sometimes of value, especially to tide over a period of severe acute failure. For this purpose the administration of 0.3 to 0.6 c.c. (5 to 10 minims) of the 1 : 1000 solution every ten or fifteen minutes for six doses is particularly serviceable. Given in this way the vasoconstrictor effects are largely avoided. The use of an ice-bag over the heart may be of some value, and at least insures periods of complete quiet to keep it in position.

During *convalescence*, rest should be continued until the heart rate remains normal and the more serious disturbances of rhythm have disappeared. Massage, passive and, later, mild active movements should be begun before the patient is permitted to sit up. Sitting up should be allowed for only a few minutes at first and the time very gradually increased. The patient should not be permitted to get out of bed until he can sit up in bed without fatigue for several hours. A nutritious, easily digestible diet should be given. Arsenic in the form of Fowler's solution or the cacodylate of sodium is often of some value. When the patient can be up and about a very gradual course of physical training may be instituted, but in the more serious cases marked exertion cannot be allowed for several months.

Chronic Myocardial Disease.—Several types of chronic disease of the myocardium are generally described, the differentiation being made on the basis of the pathogenesis or of the pathological changes in the heart muscle. This division may be reasonably satisfactory to the pathologist, but from the clinical point of view it does not seem to serve any useful purpose because the majority of cardiac symptoms and signs are common to all types, irrespective of pathology or pathogenesis. The separate clinical discussion of each of these types has tended to confuse the minds of both students and physicians, since however distinct they may be pathologically, they constitute symptomatically but a single syndrome. The inclusion of the several types under the single title of *chronic myocardial disease*, on the other hand, serves to emphasize their clinical unity and to avoid the confusion which has existed. This plan of presentation simplifies the entire subject of chronic disease of the heart muscle and obviates much unnecessary repetition.

Incidence.—Chronic myocardial disease occurs more frequently in men than in women (about 3 to 2). One-third of all cases occur between the ages of fifty-one to sixty, while three-quarters of all are found in the three decades between forty-one and seventy years. These figures are for con-

ditions without structural lesions of the valves. When those with organic valve lesions are included, the age of greatest incidence is lowered by the large group with chronic rheumatic endocarditis and myocarditis.

Morbid Anatomy and Pathogenesis.—*Chronic Myocarditis.*—The term "chronic myocarditis" has often been used loosely to designate most or all of the conditions included by the term "chronic myocardial disease." The term "myocarditis" should, however, be restricted to those conditions in which there is a productive inflammatory process in the heart muscle in contradistinction to those in which the lesion is essentially degenerative. Chronic myocarditis may develop as a late stage of the acute process, or may occur without previous evidence of the acute form. The most common *acute infections* which cause it are acute rheumatic fever, typhoid fever, influenza, the septicemias, and occasionally diphtheria. Chronic myocarditis of some degree is almost always associated with the various forms of chronic or subacute endocarditis, and is often the most important cause of heart failure in such cases.

Gross examination of the heart reveals hypertrophy and dilatation, and in some instances evidence of an increase in the quantity of fibrous tissue. Microscopically, there is round-cell infiltration in the interstitial tissues and parenchymatous degeneration of the muscle-fibers in areas where the process is active. In older lesions there is connective-tissue proliferation and degeneration of the muscle cells, which are ultimately replaced by fibrous scar tissue. The latter process may end in healing, but in many cases the processes are progressive, or the inflammation undergoes remissions and exacerbations. Chronic myocarditis may finally develop in a heart which is already the seat of old healed lesions from an earlier attack. The changes are least marked in the auricles and usually best developed in the left ventricle.

Syphilis is the only chronic, specific infection which is a common cause of myocarditis. It may produce solitary or multiple gummata, but this is rare. The lesion usually evoked is chronic, diffuse, interstitial inflammation which is generally indistinguishable from that just described. *Chronic focal infection* in the teeth, tonsils, sinuses, gall-bladder, or elsewhere may occasionally be a cause. It is difficult and often impossible, however, to establish any relationship between chronic myocarditis and such disturbances. *Tuberculous myocarditis* is extremely rare except in association with tuberculous pericarditis or general miliary tuberculosis. In both conditions the myocarditis is masked by the symptoms of the underlying tuberculous process.

Myocardial Degeneration (*Myocardial Fibrosis, Interstitial Myocarditis*).—In a majority of cases of chronic myocardial disease the lesions are degenerative in character. The commonest causes of myocardial degeneration are the *chronic vascular diseases* (general arteriosclerosis, sclerosis of the coronaries and aorta, syphilitic endarteritis, and chronic hypertension). Opinions differ as to the relative importance of these several conditions. Arteriosclerosis and syphilitic endarteritis of the walls of the coronaries or the aorta at their sites of origin narrow the lumina of these vessels and obstruct the circulation through them to a greater or lesser degree. This gradually destroys the muscle-fibers, which become fragmented and lose their nuclei. The interstitial fibrous tissue proliferates and new fibrous tissue develops to replace the destroyed muscle cells. This process leads to

the formation of scars or cicatrices. When a coronary artery is narrowed at its mouth or in one or more of its main branches the lesion is more or less diffuse in the entire area which it normally supplies; when one or more small branches are chiefly affected or completely occluded by thrombi the process is focal. Complete or nearly complete occlusion of a medium-sized branch may result in destruction involving the entire thickness of the ventricular wall, in an infarct, and the ultimate formation of a dense scar. This type of scar is called a *myocardial cicatrix*. It may stretch gradually and bulge with the production of a cardiac aneurysm. Hearts with this type of degeneration are dilated and hypertrophied. The fibrosis may not be visible to the naked eye, or small, whitish areas of fibrous tissue scattered throughout the ventricular musculature may be apparent on close examination. Such areas are most commonly found near the apex of the left ventricle and in the papillary muscles, but they may appear anywhere. The focal lesions are usually readily visible as grayish-white patches beneath the endocardium and within the ventricular wall on section.

Chronic myocardial disease due to *hypertension* causes fairly characteristic pathological changes. There is marked hypertrophy of one or both ventricles, with extensive dilatation. Some of the largest hearts are found as the result of prolonged hypertension. Macroscopically, the muscle appears essentially normal, but microscopically, there may be diffuse proliferation of connective tissue within and between the muscle bundles. The auricles are much less affected than the ventricles. They are usually greatly dilated, however, and at times undergo considerable hypertrophy. The condition known as *essential hypertension* and the hypertension associated with *chronic interstitial nephritis* are the two great causes of this type of myocardial degeneration, and are regarded by some as the most common causes of chronic myocardial disease in general. The left side of the heart is predominantly affected, but in the later stages right-sided dilatation and hypertrophy are usually also found. Involvement may be limited chiefly to the right ventricle and auricle in congenital pulmonary stenosis, in long-standing bronchial asthma or pulmonary emphysema, and under other conditions in which there is continued hypertension in the pulmonary circuit. Several theories have been propounded to account for the myocardial degeneration and fibrosis in these hypertensive conditions, but none is wholly satisfactory. Briefly, the two leading theories are that the myocardial changes are due to the direct action on the heart of the unknown toxins which are responsible for the hypertension; and that the continued excess resistance against which the heart must work impairs its nutrition and interferes with the removal of the waste products of its activity, which leads to degeneration. The former fails to explain cases in which the lesion is sharply restricted to one ventricle; the latter is supported by the well-known fact that the changes are always greatest in the ventricle most subject to increased peripheral resistance. It has recently been shown that in the majority of cases of vascular hypertension the finer arterioles, especially in the retina, are sclerotic and narrowed. It seems possible that similar changes occur in the fine arterioles of the heart muscle, but escape recognition by the usual methods of examination.

Miscellaneous Conditions.—Fatty degeneration is frequently one of the pathological changes associated with chronic myocardial degeneration. It often appears in chronic valvular disease with other evidences of chronic

myocarditis, and may be produced by prolonged severe infections and by chronic poisoning with phosphorus, arsenic, and chloroform; it occurs very commonly in severe anemia and when the heart is syphilitic. The heart may appear almost normal grossly; it may be flabby and yellowish in color. In severe anemia small patches or strips of yellow may be visible beneath the endocardium, especially in the papillary muscles and the trabeculæ (tiger heart). The fat is probably deposited in the heart to replace destroyed muscle tissue, and comes from without rather than from within the heart itself.

Fatty infiltration, or the *fatty heart*, is a part of general obesity, and is said to be especially common among excessive beer drinkers. In this condition the heart is encased in an excessively thick layer of subpericardial fat. This often penetrates into the myocardium between the muscle bundles, and may even cause degeneration and destruction of some of them. The heart is usually somewhat dilated and hypertrophied. The only symptoms are those of heart failure in an obese patient.

Symptoms of chronic myocardial disease not infrequently appear in exophthalmic goiter and toxic adenoma of the thyroid. The frequency and extent of structural change in the myocardium in these disturbances has not been adequately studied. The left ventricle, and later the whole heart, may undergo hypertrophy and dilatation. Patchy or diffuse thickening of the endocardium may occur and at times extend into the adjacent muscle. There may be some lymphocytic infiltration of the myocardium. It is probable that structural change is often absent or insignificant even when there are definite symptoms of myocardial insufficiency, since surgical relief of the thyrotoxicosis is often followed by prompt and lasting disappearance of all evidences of cardiac involvement.

The prolonged, excessive physical exertion required of professional athletes and certain classes of laborers has been thought to cause hypertrophy and chronic myocardial damage. Recent studies by Gordon, Levine, and Wilmaers on a series of Marathon runners failed, however, to reveal cardiac enlargement, even in men who had engaged in the most vigorous physical effort for many years. It seems probable that physical exertion alone does not cause myocardial damage in the absence of infection, vascular changes, or other disease.

Finally, attention must be called to the fact that all of the symptoms and signs of cardiac insufficiency may be present during life, although at autopsy no significant structural changes in the heart muscle can be found other than some degree of hypertrophy and dilatation. It is not to be inferred from this that such heart muscle is normal, but rather that present methods of study are as yet inadequate to reveal the changes which are present. In such cases, however, cardiac failure and death may be due solely to exhaustion of the heart.

Symptoms.—Chronic myocardial disease may produce no symptoms whatever, and may even be the cause of sudden death in apparently healthy individuals. Careful examination will in most cases, however, reveal abnormalities which are sufficient to establish the probable diagnosis. Close questioning also brings to light symptoms which suggest the existence of some impairment of cardiac efficiency of which the patient is unaware, such as moderate shortness of breath following stair climbing, walking against a high wind, or running a short distance. Some degree of hypertrophy and

dilatation is almost invariably associated with chronic myocardial disease, even when there are no symptoms. This should be found in the course of routine examination, and should arouse suspicion of chronic disease of the heart muscle. Occasionally fibrillation of the auricles may be unnoticed by the patient, or pulsus alternans may be discovered during auscultatory determination of the blood-pressure. Finally, a routine electrocardiographic examination may reveal defects in conduction, such as bundle branch block or intraventricular (arborization) block.

Usually chronic myocardial disease evokes the common symptoms of heart failure or myocardial insufficiency. These are not pathognomonic of the condition which causes the failure. The number and severity of the symptoms varies greatly and there is no necessary relationship between their number or intensity and the nature or extent of the structural changes in the heart, although certain syndromes are more characteristic of one type of myocardial disease than of others. Anatomically slight lesions may cause severe symptoms, especially if they involve the conduction system, while extensive damage of the ventricular musculature may produce only minor symptoms of impaired cardiac efficiency. It is important to keep these facts always in mind if serious errors in diagnosis or prognosis are to be avoided.

The outstanding manifestation of chronic myocardial disease is the circulatory deficiency and stasis which is directly responsible for most of the symptoms. Except for pain and palpitation the symptoms are not usually referred directly to the heart; those which are, are due chiefly to its exhaustion. Clinically, cardiac failure may be divided into two main types: that in which passive venous congestion prevails; and that characterized by cardiac pain.

Congestive cardiac failure is much the more frequent form and has been estimated to occur in not less than 70 per cent. of all cases. The most common initial symptom is *breathlessness following exertion*. Since the normal susceptibility to breathlessness varies greatly, it is especially important to interpret this symptom in the light of the individual's normal response to effort. Shortness of breath, which recurs regularly upon repetition of mild overexertion, does not subside after brief rest, or is accompanied by a sense of suffocation, substernal pressure, or fulness, is generally an indication of cardiac insufficiency. This tendency to dyspnea may increase gradually, or may remain stationary for a long time. A slight cough often accompanies the breathlessness and is sometimes wrongly attributed to a cold. It is, in reality, due to slight passive congestion of the lungs.

Exhaustion and a *tendency to become easily fatigued* are frequent early symptoms. They occur especially toward the end of the day, even in the absence of any unusual activity. *Edema* is not commonly observed by the patient in the early stages of heart failure, because if it is present it is usually so slight as to escape attention readily. It is characteristically of the dependent type and is usually manifest toward evening as puffiness of the legs above the shoe tops. It shifts during recumbency so that it is generally absent from the legs in the morning. Rarely the early edema is limited to the face, especially about the eyes. Complaint of rapid beating of the heart, or palpitation, is made occasionally. Syncope is rare as an early symptom.

Advanced congestive failure may evolve gradually as cardiac exhaustion, passive congestion, and venous stasis increase. The early symptoms are

all aggravated and new ones make their appearance. Advanced failure may also develop acutely as the result of some unusual physical or mental strain, and occasionally without a discoverable precipitating cause.

The symptoms of advanced failure are referable chiefly to the respiratory and digestive systems and to accumulation of fluid in the subcutaneous tissues and serous cavities. Dyspnea is an outstanding feature. It follows any exertion, and in severe cases may be present even when the patient is at rest. *Orthopnea* usually accompanies the severer grades of dyspnea, and compels the patient to maintain an erect or semirecumbent position even in sleep. *Cyanosis* is more or less pronounced. The *cough* produced by pulmonary congestion is likely to be troublesome; it may be dry or productive of frothy, mucoid expectoration, which is sometimes tinged with blood in the more severe cases. In acute failure these symptoms may be associated with a *mild febrile reaction* which has caused the condition to be mistaken for an acute respiratory affection.

The *vital capacity of the lungs* is diminished in more or less close proportion to the severity of the respiratory symptoms and the degree of heart failure. The length of time during which the subject can hold his breath is much shortened, and some cannot stop breathing at all. Examination of the lungs reveals signs of *passive congestion*, which are usually more marked in the right lung. Moist râles are present at the bases posteriorly in milder cases, while in the severe conditions the whole of both lungs may be filled with coarse, bubbling rhonchi. All gradations between these extremes may be found. In marked pulmonary congestion there is usually diminished resonance or dulness over the lung bases, with impaired fremitus, voice, and breath sounds. When pleural effusion is present it may mask the signs of pulmonary congestion to some extent.

Digestion is usually impaired, the appetite is poor or lost, and there is gaseous distention of the stomach and bowels, usually with constipation. Nausea and vomiting are common in severe conditions and are often associated with pain and soreness in the epigastrium and right hypochondrium. Jaundice may follow congestion of the liver, but is seldom pronounced. All these symptoms are evoked by congestion and stasis in the splanchnic veins and liver. Examination usually reveals *enlargement of the liver*. The free border generally is palpable well below the costal margin, and may extend below the level of the umbilicus. It is rounded, firm, and may be extremely tender in the acute disturbances. When hepatic congestion is of long standing, tenderness is generally absent and the edge feels quite hard and smooth. Expansile systolic pulsation of the liver is not infrequent in acute failure and is positive evidence of tricuspid insufficiency from dilatation of the right heart.

Edema is a usual symptom, and is characteristically found in the dependent portions of the body: in the legs and feet when the patient is up and about; in the pelvic and lumbar regions when he is in the semi-recumbent position. General anasarca is not uncommon, but is usually most marked in the dependent parts. When the edema is extreme the distended, water-logged skin may crack and release large quantities of serous fluid. This entails great danger of infection on account of the poor nutrition of the tissues. The skin is often cold, clammy, and covered with cold sweat.

Fluid often transudes into the pleural and peritoneal cavities, rarely into the pericardium. The right pleura is affected first in most cases, and may be

the only cavity involved. Several explanations have been offered to account for this localization, the most plausible of which is that the azygos veins are somewhat compressed by dilatation of the right heart. When edema is marked both pleural sacs may contain transudate and ascites may be present. Fluid may be present in the right pleura even without edema, but this is not usual. Accumulation of fluid in the pleural spaces and abdomen aggravates respiratory symptoms by mechanical interference with breathing.

Kidney function is impaired; oliguria is often marked; and the urine is concentrated and of high specific gravity. It contains considerable albumen and all types of casts except the waxy. Urates are commonly present in excess. The excretion of phenolsulphonephthalein may be as low as 15 to 30 per cent. With the impaired renal function some nitrogenous waste products may be retained in the blood, but this is seldom marked. The content of these nitrogenous bodies is usually normal or only slightly above the upper limits of normal.

The *nervous system* is affected by the inadequate circulation which causes a sense of weakness or exhaustion and drowsiness. Sleeplessness may occur and hallucinations or delirium may develop. The memory is often impaired and mental effort may cause severe fatigue. Either depression or exaltation may be observed.

The symptoms directly referable to the *cardiovascular system* are few and relatively unimportant in most cases of congestive failure. Palpitation, fluttering, or subjective precordial beating may result from auricular fibrillation, premature beats (extrasystoles), or marked hypertrophy of the heart. There may be some precordial hyperesthesia, especially in the region of the apex. Throbbing in the peripheral arteries, particularly in the neck, is a rare complaint in the absence of aortic insufficiency.

The *physical signs in the cardiovascular system* vary greatly. Some enlargement of the heart is almost invariably present because of hypertrophy and dilatation. Since it is rarely possible to determine by physical examination which of the two factors predominates, it is customary to use the inclusive term "enlargement." With symptoms of advanced failure, however, dilatation may be assumed to be in the ascendency. The extent of enlargement varies, although it is pronounced in the majority of cases. The apical impulse is usually forcible and often heaving when there is great hypertrophy; marked dilatation, on the other hand, usually renders it diffuse and feeble. The position of the apex and the left limit of cardiac dulness are the most trustworthy physical evidences of enlargement of the heart.

The *heart rate* is commonly increased even during rest. Disturbances of rhythm are frequent; the auricles fibrillate in more than 50 per cent. of patients. This may be transitory or paroxysmal, but is generally permanent. The rate of the ventricles is usually rapid (140 or more beats per minute), and there is total irregularity of the beats both in force and in rhythm. The rate varies from minute to minute and is peculiarly subject to marked acceleration after exertion. Many of the ventricular beats are too feeble to transmit a wave to the wrist, so that the radial pulse rate is usually less than that of the heart. This difference is called the *pulse deficit*, and its degree is usually more or less parallel to the degree of cardiac failure. The radial pulse rate must never be considered an index of the heart rate in fibrillation.

Auricular flutter is comparatively uncommon. *Premature beats* (extrasystoles) are often present if the heart rate is not very high. They are characterized by their prematurity and by the long subsequent diastole. The premature systole can always be heard over the heart, but sometimes cannot be felt in the pulse. Premature beats have no significance unless they are very numerous. They may then contribute to the embarrassment of the circulation. *Complete heart-block* is not infrequent, especially in long-standing syphilitic conditions. It is easily recognized by the very slow heart rate (below 40 per minute). *Incomplete block* causes dropping of the beats which can be differentiated from premature beats by the silence of the heart during a period nearly equal to that of two normal cycles. In partial or complete block the ventricular rate may suddenly fall so low as to cause temporary cerebral anemia. The patient goes into syncope and often has a convulsion (Adams-Stokes syndrome).

The *heart sounds* are altered in various ways. If systemic blood-pressure is much elevated the second aortic sound is accentuated. The pulmonic second sound is accentuated by increased pressure in the pulmonary circulation with or without signs of passive congestion of the lungs. The first sound at the apex may be increased when there is ventricular hypertrophy, or it may be diminished and of poor muscular quality in dilatation. It is sometimes impure and often split. The occasional reduplication of the second sound causes a gallop rhythm.

Murmurs may or may not be present. They are due to an associated valvular lesion caused by preceding endocarditis or to extensive dilatation of the heart with resulting functional incompetency of the valves. Differentiation between the two is difficult and may be impossible. Dilatation of the left heart often produces functional mitral incompetency evidenced by signs identical with those of incompetency due to mitral endocarditis. Rarely extreme dilation renders the aortic valves incompetent by stretching the aortic ring. Incompetency of the tricuspid valve occurs very frequently when the right heart is dilated. It may produce the typical systolic murmur over the lower end of the sternum, but a murmur is often absent.

Cardiac Pain.—The *pain* of chronic myocardial disease occurs characteristically in paroxysms which are *induced by effort or emotional stress.* It is located in the upper sternal region, or upper left chest, and may radiate over the whole precordium, to the left shoulder, arm, or hand, and to the left angle of the jaw. Rarely it extends to the right side. It varies in severity from moderate discomfort to pain of the most agonizing type, and is described as a feeling as if the heart were being squeezed in a vise. This is generally accompanied by a sensation of constriction of the chest and a feeling of impending death. The paroxysm is usually associated with vasomotor phenomena, such as pallor of the face and a profuse cold sweat, or congestion and suffusion of the face. The attacks seem especially prone to follow exertion shortly after a meal, probably because the diversion of a large proportion of the blood to the splanchnic area reduces the supply to the heart. The attacks never occur when the patient is at rest or asleep until the later stages of the disease. They may then occur at very frequent intervals without any apparent provocation. This condition has been termed the *status angionosus.* Ordinarily the earlier attacks recur at rather long intervals, often many weeks or months apart. As the disease progresses

they become more and more frequent and are precipitated by ever-decreasing degrees of effort.

The seizures of pain generally compel immediate cessation of all efforts, even of all motion, and the heart usually recovers promptly, so that the pain passes off in a few moments. With the cessation of the attack, large amounts of gas are often expelled from both stomach and bowels, and there is often profuse flow of pale urine of low specific gravity. The patient is left more or less exhausted and often suffers from numbness in the left arm after the severe pain. The painful areas are usually hyperesthetic to squeezing, pressure, or the prick of a sharp object. They are the zones of sensory distribution of the fifth cranial nerve, the second, third, and eighth cervical, and the first four thoracic nerves. Since the spinal segments from which these nerves arise are those to which the cardiac sympathetic fibers pass, the pain and hyperalgesia are merely expressions of the cardiac viscerosensory reflex. Nausea and vomiting are also probably produced reflexly by the heart. Rarely the attacks of pain last an hour or more, but pain which continues without remission for more than an hour or two is generally due to coronary occlusion. The term "*angina pectoris*" is used to denote these particular attacks of pain and the phenomena characteristically associated with it. The name is often employed erroneously to designate a disease entity, despite the fact that heart pain is merely a symptom. This misuse of the term has caused much confusion and misunderstanding. A detailed discussion of the syndrome is to be found in the section on Angina Pectoris.

The *respiratory symptoms* in patients with heart pain are quite different in character from those of congestive failure. During the attacks of pain there is often a sensation of smothering, although shortness of breath and orthopnea are slight or absent. Other patients suffer from paroxysms of severe nocturnal dyspnea and orthopnea, which appear spontaneously and without relation to pain. These are especially associated with aortitis and are attributed to reflexes which arise in the arch of the aorta. Patients with chronic hypertension sometimes suffer sudden nocturnal attacks of pulmonary edema. While these appear to occur spontaneously, they usually follow overtaxation of the heart by exertion, worry, or anxiety. Though very alarming they are not usually fatal.

Patients with heart pain may die suddenly during an attack, probably because of the inception of ventricular fibrillation. This form of death is relatively uncommon, especially during the first seizure. When it does occur, it is usually due to closure of one of the main branches of a coronary artery by thrombosis. Some patients die of progressive cardiac exhaustion several hours after an attack of pain. Many develop auricular fibrillation which evokes congestive failure due to increased cardiac exhaustion. With the onset of congestive failure the attacks of pain and paroxysmal nocturnal dyspnea cease.

Physical examination of patients with pain reveals comparatively little except the hyperesthesia already described. Enlargement of the heart is usual, but not often pronounced. The aortic second sound may be accentuated and the first sound at the apex may be of poor muscular quality. Murmurs are usually absent. The rhythm is regular except for the occurrence of premature beats, which are fairly common. The peripheral arteries may be thickened if there is arteriosclerosis, or there may be hypertension.

Pulsus alternans is common, especially immediately after an attack or in the later stages of the disease. It is usually an unfavorable sign.

Course and Prognosis.—Chronic myocardial disease is almost invariably progressive, but the rate of progress varies greatly in different cases. Since symptoms rarely appear before some degree of heart failure has developed, the disease has usually existed for months or years before it is recognized. After the appearance of symptoms failure may be so rapid that death ensues within a few weeks or months, but it may be so slow that there is little detectable advance from year to year, and the patient lives for ten or fifteen years. Intercurrent diseases, especially acute infections, are likely to cause death or to increase greatly the rate of downward progress. The average patient lives for less than ten years after the onset of symptoms of congestive heart failure, and for less than five after the first attack of heart pain.

Prognosis should seldom be attempted when a patient is first seen during an attack of failure, but should be reserved until the extent of possible recovery has been determined. Usually it is unsafe to base prognosis on the nature or the severity of the symptoms of heart failure. The safest guide for prognosis is the estimate of the extent of cardiac damage obtained from a study of the heart's response to effort. This should be based on a careful history and on the response to strains to which the patient is unavoidably subjected rather than on so-called functional tests. The patient's age and general health must always be taken into consideration. The following signs are serious and warrant a guarded prognosis because they indicate extensive damage to the heart: poor response to moderate effort; failure to improve in response to effort after prolonged cardiac rest; pulsus alternans; Cheyne-Stokes breathing; and status anginosus.

Sudden death is always a danger, and cannot be anticipated. It is, however, almost invariably preceded by evidences of limited response to effort. It is common with auricular fibrillation, when it is most often due to embolism; and with cardiac pain, when it is due to ventricular fibrillation or to sudden cessation of ventricular activity. Almost 50 per cent. of patients with cardiac pain die suddenly, either during an attack of pain or, more often, in the absence of a paroxysm. The majority of deaths in chronic myocardial disease occur in patients between fifty and seventy years of age.

Diagnosis.—The diagnosis of chronic myocardial disease can usually be made with reasonable certainty even before heart failure develops. It is based on: the antecedent history or on the presence of conditions which accompany or cause diseases of the heart muscle, such as rheumatic fever, syphilis, arteriosclerosis, chronic hypertension, chronic interstitial nephritis, etc.; the presence of cardiac enlargement; the occurrence of certain arhythmias, especially auricular fibrillation or flutter, and pulsus alternans; and the results of electrocardiographic, polygraphic, and *x*-ray examination. Diagnosis of the type of lesions probably present in the heart is based on the history and the associated findings, and is largely a matter of inference. When heart failure has developed the characteristic signs and symptoms, in addition to the foregoing evidence, usually render the diagnosis relatively simple.

Chronic myocardial disease must be differentiated from several conditions which may produce somewhat analogous symptoms. General

weakness and exhaustion from *acute disease or in the course of wasting illness* can usually be recognized by the close association of the causative factor. As such conditions often result in myocardial disease, its presence or absence must be determined by the search for cardiac enlargement, arhythmia, or other definite evidences of cardiac involvement. In the absence of such signs it is often impossible, however, to be certain that the heart has escaped, and judgment should be suspended until the patient has been under observation and treatment for a few weeks or months.

The symptoms of *chronic pulmonary disease* may be confused with the respiratory symptoms of congestive failure, and the digestive symptoms of the latter may be mistaken for those of *acute or chronic disease of the alimentary tract.* In both cases the history and physical signs, and the occurrence in myocardial disease of enlargement of the heart and other evidences of cardiac failure should make differentiation easy.

Chronic nephritis with edema can be recognized by the absence of evidences of cardiac failure, by the distribution of the edema, and by chemical examination of the blood and tests of renal function.

Finally, *effort syndrome* must be differentiated from myocardial disease with heart pain. The effort syndrome occurs typically in young neurotic adults, and the attacks of pain are not closely related to exertion, but often begin during complete rest in bed, especially at night. In the effort syndrome the heart is not enlarged and the antecedent history is quite unlike that of myocardial disease.

Treatment.—The treatment of chronic myocardial disease is both prophylactic and symptomatic. Preventive therapy is intended either to avoid the development of myocardial disease or to check its advance, once it has developed. When a patient is suffering with any one of the common causes of chronic cardiac disease, prophylactic treatment should be instituted immediately whenever that is possible. Rheumatic fever, chronic focal infection, and syphilis can be dealt with more or less efficiently. Arteriosclerosis and chronic hypertension, on the other hand, which are the chief underlying causes of chronic disease of the heart muscle, do not respond easily to treatment, although their development may be retarded. Nevertheless unremitting attention should be given to the protection of the heart. This is best accomplished by removing all discoverable sources of infection; by sufficiently prolonged convalescence from acute diseases; by the intensive, early, and prolonged treatment of syphilis; by detailed control of diet, occupation, and general hygiene; and by insisting that the patient avoid all overtaxation of his heart. These measures should also be employed after the myocardium has become diseased, and even after symptoms of heart failure have appeared, in the hope of preventing increasing damage.

The earlier preventive treatment is instituted, the greater is the prospect of its effectiveness. Unfortunately, however, relatively few patients receive treatment until symptoms of failure have appeared. Early preventive treatment cannot become general until both laymen and physicians have learned to appreciate more fully the importance of frequent periodic medical examinations.

Symptomatic treatment is separately discussed in the section on The Treatment of Cardiac Failure.

Coronary Occlusion.—Occlusion of one of the larger coronary arteries

occurs more frequently than is generally recognized. The obstruction is almost always due to thrombosis, although in rare instances embolism may be the cause. The thrombus is generally associated with atheromatous endarteritis, which may either be confined to the coronary arteries or be part of more or less generalized arteriosclerosis. The left coronary, or one of its main branches, is the vessel most often occluded. The obstruction produces an anemic infarct of the heart, generally in the anterior, apical portion of the left ventricle, or near the base of this ventricle and in the interventricular septum. The coronaries are not strictly end arteries, but their anastomoses are usually inadequate to assume the function of a large branch, such as the descending ramus. Communication through the Thebesian vessels may supplement the direct anastomoses between the right and left coronaries.

Coronary occlusion occurs for the most part in individuals of middle or advanced age, and is relatively more frequent in those who suffer from heart pain. Herrick groups the cases into four clinical types:

1. "Cases of instantaneous death . . . in which there is no death struggle, the heart beat and breathing stopping at once.
2. "Cases of death within a few minutes or a few hours after the obstruction. These are the cases that are found dead or clearly in the death agony by the physician who is hastily summoned.
3. "Cases of severity in which, however, death is delayed for several hours, days, or months, or recovery occurs.
4. "A group that may be assumed to exist embracing cases with mild symptoms, for example, a slight precordial pain ordinarily not recognized, due to obstruction of the smallest branches of the arteries."

Symptoms.—The outstanding symptom is the *severe heart pain,* which often begins without exertion or other assignable reason. The pain may be in the areas already described, or in the region of the ensiform or upper epigastrium. It is ordinarily severe, but varies considerably in intensity. Unlike heart pain in general, the pain does not pass off rapidly, but persists for hours, sometimes for days. It is not relieved by the nitrites. Nausea and vomiting frequently accompany the pain. At the onset there are often symptoms of shock and collapse, such as ashen pallor, cold sweat, clammy skin, and a rapid, feeble pulse, which is sometimes scarcely perceptible. In spite of the intensity of the symptoms, the mind is usually clear. Low fever is common during the first few days. There is often a moderate leukocytosis with a relative increase in the polynuclear count.

Examination of the heart usually reveals enlargement, which is sometimes marked. The rate is generally rapid, but occasionally very slow. There may be partial block and premature beats are common. The sounds are often quite feeble, and a systolic murmur due to relative mitral insufficiency may be heard. The pericarditis which sometimes develops over the infarct is evidenced by a friction-rub. The blood-pressure is usually reduced and often continues to fall in severe conditions. Acute pulmonary congestion or edema are common. Later the general signs of venous stasis and passive congestion may develop.

Prognosis.—If death does not result after a few days or a week, recovery is to be expected. Recovery may be so incomplete that the patient dies from congestive heart failure in a few weeks or months. In other cases it is sufficient to allow the patient to lead a greatly restricted life for a few

years. Finally, healing may be complete, and the patient may become about as well as he was prior to the occlusion. Such cases are usually those of closure of medium-sized branches. Subsequent attacks are frequent. The electrocardiograph is helpful in confirming the diagnosis of these accidents.

Diagnosis.—Coronary occlusion must be differentiated from the more *common heart failure* with pain. The pain of occlusion is unrelated to effort, is not relieved by rest, is much more lasting, does not yield to the administration of vasodilators, and is often associated with symptoms of shock or evidences of rapidly progressing heart failure. Pain in the upper abdomen, shock, and gastro-intestinal symptoms may lead to confusion with *perforated gastric ulcer, acute pancreatitis,* and other surgical conditions within the abdomen. Differential diagnosis rests mainly on the history and the evidences of cardiac disease in the one and on the development of peritonitis in the other.

Treatment.—The essential feature of treatment is *absolute physical and mental rest.* The patient must be put to bed and forbidden to make the slightest exertion, even that of feeding himself or turning over. *Morphin* should be administered subcutaneously in sufficient quantities to control the pain (at times 65 milligrams (gr. 1) or more). *Warmth* should be insured by blankets and hot-water bottles. When *food* can be taken it should be liquid or semisolid, easily digestible, and given in small quantities. *Enemas* should be used to keep the bowels open. Circulatory stimulants are of doubtful value at the outset, but digitalis may be given cautiously, sometimes with apparent benefit. If, after a few days, heart failure sets in, it should receive the usual treatment. Rest and convalescence must continue for several weeks to allow healing of the cardiac infarct.

Cary Eggleston.

References

For references see page 1054.

ENDOCARDITIS

Definition.—Endocarditis is an inflammation of the tissue lining the cavity of the heart, particularly the tissue of the valves. The simplest classification of the different types is as follows:

1. Non-bacterial (*simple*):
   - (*a*) Acute non-rheumatic.
   - (*b*) Acute rheumatic.
2. Bacterial (*mycotic*):
   - (*a*) Acute.
   - (*b*) Subacute.

Malignant endocarditis includes those forms of the acute bacterial type which are rapidly fatal. In all types the inflammation may ulcerate. Since the lesions on the valves, except for the simple erosions, are spoken of as vegetations, the terms *ulcerative* and *vegetative* are not distinctive. The vegetations of the non-bacterial variety are called *verrucous.* The initial erosion of the valve with its deposited clot has been called *thromboendocarditis.*

Incidence.—In the medical service of Barnes Hospital there were 63 cases of acute and subacute endocarditis between 1913 and 1923. These were distributed as follows:

1. Non-bacterial:		2. Bacterial:	
(*a*) Acute non-rheumatic.	5	(*a*) Acute.....	3
(*b*) Acute rheumatic	18	(*b*) Subacute.....	18

In 15 instances a clinical diagnosis was made on the basis of a murmur in the course of a febrile disease—an uncertain diagnosis, frequently disproved at autopsy. In 4 cases the diagnosis was not made until autopsy.

Morbid Anatomy.—Erosions are the first lesions to occur, and may become infected at once or be organized into verrucous vegetations, which may either form scar tissue or themselves be later infected. Just how the rims of the valves become eroded is uncertain, but the process is apparently non-specific, because the appearance at autopsy is the same whatever the disease of which the valvular erosion was a complication.

The fact that erosion occurs in the absence of demonstrable infection (as in terminal kidney disease) seems to point to a non-infectious origin. Whether the agency producing the injury acts upon the surface of the valves or beneath the surface by way of the capillaries is unknown, but no connection between the lesion and the underlying blood supply can be shown microscopically. The final amount of vegetation and scar tissue depends upon the degree of initial injury and the number and severity of recurring injuries. At autopsy it is common to find fresh erosions engrafted on old verrucous vegetations. In rheumatic fever such recurrences are apt to be frequent, and the consequent scarring and contraction dense and destructive of valve function. Both the erosion and the verrucous vegetation are susceptible to bacterial implantation. It is important to regard bacterial infection as a secondary phenomenon, which may take place either during the original disease which caused the erosion or later on in life. Thus, during severe pneumonia the erosions may be immediately infected by the pneumococcus in the blood-stream and produce an acute bacterial endocarditis; or this immediate invasion may not take place and a streptococcus may later infect the tissue during an attack of tonsillitis.

(*a*) Simple erosions, the earliest lesions on the valves, consist macroscopically of very small swollen areas on the rim of the valve, covered with a small delicate blood-clot. Smears taken from these lesions contain fibrin and red blood-cells, but no bacteria. Microscopically, the lesion appears as simple loss of substance on the edge of the valve with deposit of fibrin and red blood-cells. At the base of this erosion there is usually an active round-cell infiltration.

(*b*) Verrucous Vegetations.—Macroscopically, verrucous vegetations are firm, white, nodular swellings along the rim of the valve which vary in size from 0.5 to 2.0 mm. Microscopically, they are composed of a homogeneous pink-staining "fibrinoid" material surrounded by a zone of round-cell infiltration. These vegetations do not contain bacteria. In the early lesions of *rheumatic endocarditis*, underlying perivascular proliferations resembling Aschoff bodies are frequent. In their later stages the nodular appearance is lost in the diffuse thickening and puckering of the valve. Fresh erosions may develop on these vegetations at any time.

(*c*) Bacterial vegetations differ sharply from the verrucous. In gross appearance they measure from 1 to 15 mm. in diameter. When washed

free from their enmeshed blood they are sponge-like or coral-like in structure and show formations obviously guided by the currents about them.

They are gray in *color*, but the firmly attached clot gives them a reddish-brown appearance. They are *friable* and crush easily between the fingers. They are composed entirely of fibrin and bacteria. At their bases there is active organization of the tissues of the valve. There may be evidence in the neighboring valve tissue of old verrucous vegetations, and fresh erosions may be seen elsewhere on the valve.

NON-BACTERIAL ENDOCARDITIS

Simple erosions are noticed at autopsy in many conditions, such as chronic nephritis and carcinoma, in which a long period of debility preceded death. This type of endocarditis is not diagnosed during life. Such erosions may also occur simultaneously with verrucous vegetations. There is little or no clinical evidence of the existence of this type of endocarditis, and frequently when the clinician assumes, because of a systolic murmur noted during a terminal or febrile process, that such endocarditis exists, subsequent autopsy may reveal no valvular lesions. In short, a diagnosis of simple erosion can be made only at postmortem examination.

Frequently, however, during the course of a *severe infection* (acute gonorrheal sepsis, pneumonia, or meningitis) when a murmur develops which is accompanied by cardiac pain and palpitation, dyspnea, and sometimes edema of the ankles, the diagnosis of acute endocarditis is justified. In other words, the diagnosis of acute endocarditis of whatever type can be made only if some sign of cardiac failure is added to the murmur and fever. The lesions characteristic of this type are verrucous vegetations which frequently cause greater damage to the valves than do those of rheumatic endocarditis. Frequently a patient past middle age, with no history of heart disease or rheumatic fever, presents signs of marked valvular deficiency which began after an attack of pneumonia in the previous year. Any severe infection may cause such injury to the valve.

Acute Non-rheumatic Endocarditis.—Of great interest is that type of endocarditis which is not apparently in any of the foregoing classes and reveals itself as an independent disease. It is definitely non-rheumatic, since microscopical examination of the heart muscle fails to reveal any evidence of rheumatic myocarditis. Such cases are not uncommon. Mitral lesions are the most frequent, and the most extreme grade of mitral stenosis may result.

Symptoms.—Sudden *onset* with epigastric pain and vomiting, accompanied by fever and followed in one or two days by shortness of breath, slight edema of the ankles, and marked prostration are the usual initial disturbances of endocarditis. On examination a systolic murmur of mild degree is found, with signs of dilatation of the heart. Pericarditis with effusion is simulated. Moderate leukocytosis is present. The electrocardiogram shows no evidence of myocarditis. With the lapse of time the involvement of the valve becomes more apparent, particularly after acute dilatation, as shown by percussion and *x*-ray, has subsided. The acute symptoms subside in a week, but leave the patient incapable of exertion. The blood culture is sterile throughout the disease.

Diagnosis.—During the first twenty-four hours the diagnosis can

scarcely be substantiated by the evidence at hand. Such signs of cardiac disturbance as precordial pain, palpitation, moderate dyspnea, and prompt swelling of the feet on exertion determine the diagnosis.

Treatment.—Application of an ice-bag over the precordium and administration of morphin are the chief immediate therapeutic measures. Much has been said of the necessity of prolonged rest. It is always difficult to carry out this form of treatment in the case of young patients; and rest in bed for three months may apparently not prevent the progress of the disease. Nevertheless every attempt must be made to enforce rest as long as moderate exertion causes such definite cardiac disturbances as rapid pulse, weakness, dizziness, or shortness of breath.

Acute rheumatic endocarditis is almost constantly associated with acute rheumatic fever and contributes special importance to this disease.

Bacteriology.—The etiology of acute rheumatic fever is unknown, and the lesions on the valves are not infected by any bacteria which can be isolated by present methods. The occasional occurrence of non-hemolytic streptococci in the blood is interesting and may represent abortive attempts at implantation in the fresh valve lesions. The origin of such bacteria in the blood is most probably to be found in the inflammation of the pharynx which is so frequent during acute rheumatic fever.

Morbid Anatomy.—Erosions are frequently found at autopsy superimposed on chronic rheumatic endocarditis. The mode of production of the original verrucous lesions is not certain. Swift, who has given a clear conception of the pathogenesis of acute rheumatic fever, has observed perivascular proliferation in the base of rheumatic verrucæ which resembles the lesions in the heart muscle—the so-called Aschoff bodies. This suggests that perivascular subendocardial proliferations may have been the cause of the verrucous lesions. This microscopical feature distinguishes rheumatic endocarditis from other forms. In contrast to the bacterial forms, this type of endocarditis does not produce lesions elsewhere in the body, such as petechiæ and infarcts.

Symptoms.—While the signs of endocarditis, which are chiefly fever and such cardiac disturbances as palpitation, precordial pain, dilatation, or peripheral edema, are usually accompanied by acute rheumatic fever, it is possible for them to appear without rheumatism. In such cases either there is a history of preceding rheumatism with subsequent heart disease, or the patient develops disease of the joints while under observation. In the majority of cases the joint disease and valvulitis are coincident. It is difficult to determine by symptoms alone the onset of endocarditis during an attack of acute rheumatic fever. Murmur and precordial pain, increased pulse rate, and cardiac dilatation may develop overnight. The general discomfort of the patient is greatly increased and the fever curve rises. Electrocardiographic changes have been observed early in acute rheumatic fever (Cohn and Swift), and the clinical severity of the disease undoubtedly depends more on the myocardial than on the endocardial damage.

The leukocyte count is frequently 10,000 or 12,000 and a relative lymphocytosis is usually observed. Blood-cultures sometimes yield non-hemolytic streptococci, but the occurrence of these organisms is inconstant, and more than one variety of non-hemolytic streptococcus may occur in a given blood-culture. At autopsy there are no bacteria in or upon the vegetations. The dilatation of the heart is frequently so great that peri-

cardial effusion is suspected. The precordial pain is perhaps due to the pericardial inflammation which is so commonly associated with this disease.

Diagnosis.—The history or presence of acute rheumatic fever is almost conclusive evidence that the endocarditis is rheumatic. Because of the pathology of the disease, it is difficult to understand how rheumatic endocarditis could exist, except as an exacerbation of pre-existing endocarditis or as a complication of acute rheumatic fever.

The study of repeated blood-cultures is often necessary to exclude bacterial endocarditis with accompanying inflammation of the joints. To distinguish between cardiac dilatation and pericardial effusion, attention must be paid to the relative positions of the apex impulse and the outer cardiac dulness. When the sounds are clearly heard and felt as far out as the left border of the heart, as determined by percussion, there is cardiac dilatation. The fluoroscope should be employed as an aid to diagnosis of pericardial effusion.

Treatment.—Patients with acute rheumatic fever should be kept at rest with an ice-bag over the precordium. Salicylates apparently have no preventive or curative effect on the cardiac complications. Long enforced rest is as necessary as in acute non-rheumatic endocarditis. It is important that patients avoid exposure to cold and wet. When the cardiac involvement dates from an attack of acute rheumatic fever in childhood which never recurred, an adult may persistently have a murmur without any other signs of cardiac embarrassment.

BACTERIAL ENDOCARDITIS

Acute Bacterial Endocarditis.—Etiology.—Acute bacterial endocarditis develops both as a complication of such infections as pneumonia in which immediate infection of valvular erosions is presumed to occur, and as secondary infection of an older cardiac injury during the course of a bacteremia of different origin. Among the cases at Barnes Hospital, one was of the former variety and two of the latter. Autopsies on the last two revealed syphilitic aortitis with infection of the aortic valve as the preceding injury in one case, and chronic verrucous lesions as the preceding injuries in the other.

Bacteriology.—*Staphylococcus aureus*, *Streptococcus hemolyticus*, and *Pneumococcus* are the organisms especially prominent in the etiology of acute bacterial endocarditis. The malignant character of the disease with its comparatively brief course is no doubt associated with the virulence of these bacteria. Infection by the gonococcus and the influenza bacillus has also been described.

Morbid Anatomy.—Besides the lesions typical of the endocarditis there are other changes characteristic of this acute bacterial form which are usually regarded as being embolic in origin. They consist of hemorrhages about terminal vessels and subsequent infiltration with polymorphonuclear leukocytes. These lesions occur in the skin as petechiæ and on the surface of the kidney as rather coarse red spots (1–3 mm. in diameter), usually with whitish centers. Infarctions in organs such as the spleen, lungs, and brain are common. Meningitis secondary to the brain lesions occurs frequently.

Symptoms.—The type of *onset* is influenced by the character of the disease which caused the bacteriemia. Thus, if endocarditis is a complication

of lobar pneumonia it may be impossible to state exactly when the infection of the heart valve occurred. A staphylococcus infection of the valve may have entered the tissue through a trivial cutaneous abrasion, which might have sealed before the patient was examined. The *signs of sepsis* are more prominent than those of cardiac failure. High fever of the remittent type, a leukocyte count of 15,000 in streptococcus and staphylococcus infections or of 30,000 in pneumococcus infections, frequent chills, errant pains about the body, and violent cardiac action with a coarse murmur are the signs which indicate a bacteriemia fed by an infected valve. Occasionally besides petechiæ, hemorrhagic areas appear about the extremities. Signs of meningitis are common and delirium is invariably established later in the disease. Embolic pneumonia develops frequently. The average length of the disease is four weeks.

Diagnosis.—The symptoms of septicemia with special signs indicative of cardiac involvement are important in diagnosis. The most conclusive evidence is contained in the blood culture: this is invariably positive, and may be the only means by which other sources of acute infection are excluded. Positive cultures may also be obtained from the urine and spinal fluid.

Treatment.—There is no successful treatment for acute bacterial endocarditis. *Antipneumococcus serum* or its extract should be administered in large doses to patients with a pneumococcus infection. In the other cases, intravenous injection of *mercurochrome* or *gentian violet* may be tried, but there is little evidence of their effectiveness

Subacute bacterial endocarditis, which was described by Schottmueller and also by Libman in 1910, is more important than the acute type, on account of its comparative frequency. The average hospital of 200 beds, probably admits about 4 cases annually, and in localities where rheumatic heart disease is common, a larger number. With increased facilities for clinical bacteriology it is being more frequently recognized.

Etiology.—Two factors are apparently essential in every case—a preexisting injury of the valve, and a recent infection which may invade the blood-stream. In a typical case, a patient with rheumatic endocarditis and valvular heart disease suffers from tonsillitis, abscesses of the teeth, or otitis media. Under these conditions, bacteria prevalent about the focal disease may enter the blood-stream and invade the damaged valve. It may be necessary to assume that fresh erosions of the valve have occurred. In older patients atheromatous changes in the aorta and aortic valve, as well as non-rheumatic forms of chronic endocarditis, may constitute the preceding damage. Congenital defects of the heart are also easily infected.

Morbid Anatomy.—Minute perivascular hemorrhages occur throughout the body. These are soon infiltrated by polymorphonuclear leukocytes, then by lymphocytes, and finally are resolved into minute scars. They appear as crops of petechiæ about the extremities, and on the conjunctival and buccal mucous membranes. On the surface of the kidney they produce what Libman has called a "flea-bitten appearance." They are numerous in the brain and heart muscle, and on endothelial surfaces. It has been frequently assumed that these small lesions are bacterial infarctions. No definite proof has, however, been furnished regarding their exact origin. Other perivascular lesions appear which are larger and occur about the joints and produce redness and pain in circumscribed areas, with occasionally an ef-

fusion into the joint cavity. Of special interest are the partial thromboses of glomeruli which cause in this disease a peculiar form of glomerular nephritis. Infarctions of the spleen are constant and cerebral embolism is common and usually terminal.

Bacteriology.—The non-hemolytic streptococcus is responsible for about 95 per cent. of the cases of this type of endocarditis. In the 18 cases at Barnes Hospital a Gram-negative diplococcus infection occurred once and a *Staphylococcus albus* infection once. Unidentified Gram-negative bacilli and Gram-negative diplococci have been reported as the infecting organisms.

Whatever the type of bacteria, the virulence is always low. They usually incite a low-grade serological immunity which may be demonstrated by the agglutination and complement fixation tests.

Symptoms.—The *onset* is usually insidious. An increasing lassitude with moderate fever, an increasing pallor and palpitation may lead to a variety of diagnoses, such as tuberculosis or pernicious anemia, and several weeks may elapse before attention is finally focused on the heart. Very often a routine blood-culture leads to the correct diagnosis early in the disease. Petechiæ appear and a sharp pain in the upper left quadrant bespeaks the first splenic infarct. The murmur grows in loudness and coarseness. Red blood-cells appear in the urine from time to time, and positive cultures may be obtained from catheterized urine. The kidney function is little disturbed until near the end of the course. The pallor of the patient is slightly greenish if a *Streptococcus viridans* is present, and the blood-serum is similarly tinted. "Café-au-lait" is an expression used by Libman to describe the peculiar pallor of these patients. Moderate anemia is present. Pain in the toes and finger-tips is emphasized by Osler, but occurs in the non-bacterial forms as well. Dyspnea and orthopnea may occur, but rarely pneumonia. Edema of the extremities appears comparatively late in the disease. Cerebral embolism is usually the terminal event.

Little difficulty is experienced in obtaining positive blood-cultures. A feature of the bacteriology is the uniformity of the bacteriemia. A given number of colonies per cubic centimeter of blood develops consistently throughout the illness, but is not an index of the prognosis. One patient lived fourteen months while 1200 colonies developed per cubic centimeter of blood, while another lived only three months although each cubic centimeter produced only 8 colonies. A leukocyte count of 12,000 to 18,000 is common.

Diagnosis.—During any obscure fever with heart murmur the blood should be cultured repeatedly. This is the most effective diagnostic procedure. When signs of infarction or the familiar petechiæ appear the diagnosis is easily made clinically. Subacute bacterial endocarditis is to be distinguished chiefly from *rheumatic endocarditis* in which the blood contains the *Streptococcus viridans*. Subsequent cultures are negative in rheumatic cases and the course of the disease with usual recovery confirms the distinction. Furthermore, the signs of myocardial infection are not as pronounced in subacute bacterial endocarditis as in acute rheumatic endocarditis.

Prophylaxis.—In order to avoid the disease anyone known to have valvular lesions should take all precautions to prevent infections of the teeth, tonsils, and middle ear, and should have existing foci of infection removed.

Treatment.—No form of treatment is successful. It seems certain that no attempt should be made to *immunize* the patient by vaccines, serums, or non-specific "shock," since such measures seem to shorten life. Mercurochrome, acriflavine, and gentian violet have been used without avail.

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CHRONIC VALVULAR DISEASE

Chronic valvular disease of the heart consists of chronic structural change in one or more heart valves. Functional valvular defects should not be included under the term "valvular disease"; they must, however, be considered in discussing the differential diagnosis of organic defects. Myocardial failure also should not be included although most text-books in the past have done so, particularly where the treatment of chronic valvular disease is concerned. Nor will acute and subacute inflammatory processes be discussed, since the term "chronic valvular disease" refers to deformed valves and not to the diseases causing the deformity. These diseases, which are acute and subacute endocarditis, syphilis, and arteriosclerosis, are described elsewhere in this book.

History.—The first mention of the heart valves on record is in a spurious Hippocratic treatise on the heart, probably composed in the fourth century before Christ. During that same century Aristotle himself described the heart as having three chambers, but failed to mention the valves. Erasistratus of Alexandria (about 300 B. C.) gave the first good description of the valves and *chordæ tendineæ* of the heart. He introduced the names tricuspid and sigmoid. Galen (131–201 A. D.) described the valves and said that they did not close perfectly. Mundinus of Padua in 1316 wrote a remarkable description of the heart valves and their action. Since this time there have been many anatomical and physiological accounts.

The first detailed descriptions of chronic valvular disease of the heart appeared during the 17th and 18th centuries. In 1669 Mayow described the heart of a young man who died after several years of palpitation, dyspnea, and syncopal attacks. He found that the right ventricle was hypertrophied and dilated and that the mitral orifice was almost completely closed by a "cartilaginous product." In 1705 Cowper described aortic regurgitation with the occurrence of thickened, stiffened valves which "did not apply adequately to each other, whence it happened sometimes that the blood in the great artery would recoil and interrupt the heart in its systole." Hunauld in 1735 gave an excellent account of the discovery of mitral stenosis in a woman, "whose mitral valves he found beginning here and there to be ossified, and so glued together, one with another, that, the passage of the blood into the ventricle being straightened, the left auricle was consequently enlarged."

Morgagni published his remarkable collection of case histories and autopsy findings, "De Sedibus et Causis Morborum," at Padua in five books in 1760. He described cases showing lesions of all heart valves, particularly in Articles 9, 12, and 14 of Letter XXIII, of Book II on Diseases of the Thorax. Among others was a good account of a woman

with aortic stenosis and regurgitation. Also in Article 14 he reported the finding by his master Valsalva of a case of pulmonic stenosis in a girl. Symptoms, principally palpitation, dyspnea, and dropsy, frequently occurred in these cases reported by Morgagni, the autopsy findings of which are given in detail, but the only physical signs noted were dilated, pulsating cervical veins and arteries, and large heaving hearts, orthopnea and edema.

Endocarditis as a disease process was itself first clearly described by Matthew Baillie and by Allan Burns at the beginning of the 19th century. The recognition of physical signs and the discovery of instrumental methods of examination for the study of cases of chronic valvular disease were largely a development of the 19th century. At about the same time that Morgagni was publishing his case records Leopold Auenbrugger (1722–1809) in Vienna was introducing percussion of the thorax, but it was not until 1808, when Corvisart revived this discovery of Auenbrugger, that percussion began to be used widely.

The most important method of study in chronic valvular disease of the heart is auscultation. Although thrills had undoubtedly been felt by palpation with the hand, and sounds and murmurs heard by the naked ear, it was not until Laennec invented the monaural stethoscope, in 1821, that any definite progress was made in auscultation. C. J. B. Williams, in 1829, invented the first binaural stethoscope, using lead tubes fitted into a mahogany chest piece. Camman in 1851 introduced the flexible binaural stethoscope into the United States.

The first careful investigation of heart sounds and murmurs was made by C. J. B. Williams, who published in 1828–1835 three editions of a work entitled "The Pathology and Diagnosis of Diseases of the Chest, Illustrated Especially by a Rational Exposition of Their Physical Signs, with New Researches on the Sounds of the Heart." It is of much interest to note that he described with a remarkable degree of accuracy the character and the cause of the murmur of mitral stenosis. Since even at the present day many physicians are not well acquainted with either the character or the cause of the typical murmur of mitral stenosis, it is fitting that Williams' original description of nearly one hundred years ago be quoted:

"Obstructive disease of this valve commonly consists in an adhesion together, or ossification, or rigidity of some of its parts; or in a thickening and contraction of the fibrous ring at its base. It may cause a murmur with the diastole of the ventricle, and therefore, at the time of the second sound; for although the ventricle in itself produces no sound, yet, when the orifice, by which it becomes refilled, is contracted, the current being partially resisted in passing through, may become sonorous. This will therefore leave the result much as Laennec represented it, inasmuch as there is a current from the auricles to the ventricles during the diastole of the latter, although this current is not produced, as he supposed, by the contraction of the auricles. But the results of my late experiments must modify the statements of both M. Laennec and Dr. Hope, in this respect, that the contraction of the mitral orifice with its impeded current and attendant murmur, will not necessarily supplant the second sound, inasmuch as this sound is seated in the semilunar valves, the action of which may still be perfect."

Elliottson, Vauvel, Austin Flint, Graham Steell, and T. Fisher have during the middle and latter parts of the 19th century made further observations on heart sounds and murmurs, while accurate time relations have been secured during the past twenty years by the use of graphic records (phonocardiography), in particular by Einthoven, Horatio Williams, Lewis, Wiggers, and Bridgman.

During the first quarter of the 20th century there has been introduced the accurate and helpful study of the heart in size, shape, and action by means of the *x*-ray, fluoroscopy, teleroentgenography, and orthodiagraphy. The names of Groedel, Bordet, and Dietlen particularly have been connected with this development.

Finally, the introduction of graphic methods of recording the heart beat has been of value in the study of chronic valvular disease. Marey's sphygmograph introduced soon after the middle of the 19th century was later developed and amplified by Jaquet and Mackenzie. Einthoven's string galvanometer (1903) (the electrocardiograph) has been of especial value. Its records have been correlated with the findings in chronic valvular disease by Einthoven himself, by Lewis, and by the pupils of both of these pioneers.

Incidence.—Chronic valvular disease of the heart is common and is found universally. It has been estimated that about 0.5 per cent. of the community is affected. This figure is, doubtless, too high for those parts of the world where the rheumatic infections are not common, but may not be far from correct in regions where rheumatic fever and chorea are common, such as the northeastern United States of America and northern Europe, especially Great Britain. Accurate statistics are not yet available.

Lesions occur in both sexes and at any age, from birth, with its pulmonary stenosis, to senility, with its sclerotic valves. It is probably most com-

mon between the ages of fifteen and twenty-five years, when the incidence of rheumatic valvular disease is maximal, that is, in those parts of the world where the rheumatic infections are rife. At this age the female is more frequently attacked, but as an accompaniment of syphilis and arteriosclerosis the disease appears more often in the male.

Chronic valvular disease is found in all races and countries but, as has been already noted, it is commoner in colder climates.

Etiology.—There are five types of chronic valvular disease: congenital, rheumatic, syphilitic, subacute and chronic infectious endocarditis, and arteriosclerotic. The very rare involvement of the heart valves by neoplasms need not be included under the heading of chronic valvular disease. Traumatic disease of the valves may occur and proved ruptures of aortic and mitral valves are on record, but they are very rare and almost always superimposed on other diseases of the valves (rheumatism, syphilis, or arteriosclerosis). Tuberculous involvement is extremely rare.

Congenital valvular disease consists almost solely in pulmonic stenosis, which is a defect in fetal development, the cause of which is not fully known. Fetal endocarditis has been considered a reason for some cases of pulmonic stenosis, but in other cases mal-development is doubtless the cause. Congenital mitral stenosis and tricuspid stenosis have been reported but are extremely rare and undoubtedly due to fetal endocarditis. Congenital abnormalities, such as bicuspid and quadricuspid aortic valves, need not be further discussed here.

Rheumatic valvular disease results from acute infection of the "rheumatic" type, most commonly from rheumatic fever and chorea. Vague pains in the joints or muscles, tonsillitis, and scarlet fever may also cause chronic disease of the heart valves of the rheumatic type. In a certain percentage of cases, probably about one-quarter, it is not possible to obtain a clear history of any of these infections. Whether in these cases the infections themselves may be so slight that they are not noticed by the victims, whether the infecting organism may gain entrance to the circulation without producing any noticeable local or general reaction, or whether other diseases may be responsible, we do not know.

Probably nearly three-quarters of all persons with rheumatic fever or chorea develop chronic deforming valvular disease of the heart. This generally begins in childhood, is found most commonly in the decade from fifteen to twenty-five years of age, and is relatively infrequent after fifty years of age because its victims do not usually reach this age.

The infective agent in rheumatic fever and chorea is not known. It is probably the same for both diseases.

Syphilitic valvular disease results from a spirochetal invasion of the aorta which spreads down over the cusps of the aortic valve and even to the anterior cusp of the mitral valve. It occurs much more frequently in males than in females (9 out of 10 cases) and generally develops between the ages of thirty-five and fifty, some fifteen to twenty years after the primary syphilitic infection.

Miscellaneous Infectious Chronic Valvular Diseases.—Other varieties of infectious chronic valvular disease are less common. Acute and subacute bacterial endocarditis is not rare but since it is generally fatal, ensuing chronic valvular defects are unusual. Very rarely does a case of acute endocarditis due to pneumococcus, gonococcus, meningococcus,

streptococcus, staphylococcus, influenza bacillus, or other virulent organism survive, so far as is known, the endocarditis being a part of a terminal infection during severe pneumonia, meningitis, influenza, erysipelas, or other septicemia. Some evidence has recently come to light that there may be recovery from the subacute bacterial endocarditis due to the *Streptococcus viridans*, with final scarring of the valves. Typhoid endocarditis is almost unknown. Tuberculosis of the endocardium is also extremely rare; once in a great while the presence of a tubercle on a heart valve is reported. There is no evidence that such diseases as smallpox, chicken-pox, measles, whooping-cough, mumps, diphtheria, dysentery, cholera, plague, typhus, leprosy, yellow fever, beri-beri, or malaria are associated with endocarditis.

Sclerotic valvular lesions may occur in general arteriosclerosis in the old and middle aged. They may be found directly, apparently as the result of tissue degeneration following coronary sclerosis, or, as not infrequently happens, they may be superimposed on previous infectious injuries.

Morbid Anatomy.—The Valves.—*Congenital valvular disease* consists generally in the narrowing of the pulmonic valve ring, very rarely in stenosis of the tricuspid, aortic, or mitral valve. Sometimes the so-called pulmonic stenosis is located low in the heart and involves the infundibulum of the right ventricle and not the valve. This results in a two-chambered right ventricle, the terminal chamber being very small.

Chronic rheumatic valvular disease is a scarring of the cusps and even of the *chordæ tendineæ*. There is a thickening of the borders of the cusps; later a stiffening and adhesion of the cusps to one another, often with considerable deformity which may extend to the ring of insertion of the cusps; and finally a fusion of the whole valve into one fibrous mass which leaves but a narrow funnel-shaped, button hole, or fish-mouthed opening in the valve. Hardening even to the point of calcification may occur, especially in cases of long-standing aortic stenosis and mitral stenosis. The most marked lesion is usually found in the mitral valve, but is also common in the aortic valve, much less so in the tricuspid, and very rare in the pulmonic valve. The relative frequency with which these various valves are attacked is about as follows: mitral 100, aortic 50, tricuspid 25, pulmonic less than 1.

When the valve is so deformed that it can no longer close completely, regurgitation, or insufficiency, is said to be present; and when the deformity causes obstruction of the normal onward flow of blood, stenosis is said to exist. Any one of the four valves may show regurgitation or stenosis or both, and not infrequently more than one valve is defective in a single individual. The so-called functional regurgitation, or leaking, and the rare relative stenosis—both due to dilatation of the ventricles, the great vessels, or the valve rings—are not included in this discussion since in themselves they are not evidences of chronic valvular disease although they often accompany it. Anatomically speaking, organic stenosis of a valve is probably impossible without some regurgitation and vice versa; but practically there may be stenosis alone or regurgitation alone in a valve. These cases are not so common as was once thought, especially so-called pure mitral regurgitation of rheumatic origin. The frequent discovery of a mitral diastolic murmur in such cases has indicated this fact, as have also autopsy findings.

A normal heart weighing between 200 and 300 gm. should have valves with approximately the following circumferences:

	Cm.
Mitral	10
Aortic	7
Tricuspid	12
Pulmonic	8

If the mitral valve measures less than 7.5 cm. in circumference, the aortic valve less than 5 cm., the tricuspid less than 8 cm., and the pulmonic less than 6 cm., definite stenosis should probably be demonstrable clinically in a heart of average adult size.

The fact that *mitral stenosis* of rheumatic origin is as common as, or more common, than organic mitral regurgitation has not been recognized until very recently. The occurrence of both stenosis and regurgitation of the mitral valve in the same heart is certainly more frequent than the appearance of either alone.

Aortic regurgitation is about ten times more common clinically in rheumatic heart disease than is aortic stenosis. Sometimes the two are combined; and rather infrequently aortic stenosis occurs alone.

Tricuspid regurgitation is not so common an organic defect as is mitral regurgitation, while tricuspid stenosis is clinically decidedly rare both as compared to mitral stenosis, and absolutely. Slight scarring of the tricuspid valve, probably sufficient to produce slight regurgitation not demonstrable clinically, is fairly frequent, but extensive alteration in the valve is decidedly rare.

Pulmonic regurgitation is extremely unusual in rheumatic heart disease. Stenosis of the valve of rheumatic origin is very, very rare.

Often the mitral valve is the only valve diseased after a "rheumatic" infection, but in about a third of the cases with mitral involvement the aortic valve is also affected. About one-third of the cases showing aortic valve disease of rheumatic origin have no demonstrable mitral valve disease. The tricuspid valve, which is rarely involved alone, is almost always damaged at the same time as the mitral valve and the injury is sometimes accompanied by disease of the aortic valve in addition. Pathological examination shows that in 20 to 25 per cent. of the cases of mitral disease there is tricuspid disease which is not demonstrable clinically. The pulmonic valve in rheumatic infection is never the only valve affected.

Recurrent attacks of rheumatic endocarditis are so common that the valves may bear the scars of several lesions. Generally a progressive crippling develops in such cases to cause marked deformity of the valves. At times postmortem examination reveals a row of fine nodules near the edge of the valve which is indicative of an acute rheumatic endocarditis, or it may show a thickened fibrous cusp already contracted, with shortened, stiffened *chordæ tendineæ*. In rare cases Aschoff bodies (the typical subminiary nodules of rheumatic infection) have been found in the valve substance before any deformity at all has occurred.

Chronic syphilitic valvular disease presents the pathological picture of a progressive infectious process, not only the scarring but also the acute changes. The luetic lesion begins in the aorta just above the valve, and in time extends down to the mouths of the coronaries and to the valve

cusps themselves. Degenerative changes, retraction, stiffening, fusion, and finally even calcification occur. Regurgitation is the usual result and may be still further increased by a weakening and dilatation of the aortic ring. Stenosis of any pronounced degree is rare, much less common than in the case of rheumatic involvement of the aortic valve. With destruction of the valve, rupture may produce unusual signs. The loud basal systolic murmur heard over the aortic area in many of the hearts with syphilitic aortic valve disease is not caused by aortic stenosis or by aortic roughening, but by dilatation of the aorta. Rarely the syphilitic process may, by encroaching on the anterior cusp of the mitral valve, produce slight deformity, but there probably is no primary syphilis of the mitral valve. Neither is there a primary luetic lesion of the tricuspid or pulmonary valves, although unusual cases of syphilis of the pulmonary artery are on record (Ayerza's disease).

Other infectious valvular disturbances involve the valves in a variety of ways. In the case of *acute bacterial endocarditis* there is generally extensive ulceration and formation of vegetations; the edges of the valves are fringed at times with masses of bacteria and fibrin in various stages up to full organization. Any one of the valves may be attacked but the mitral and aortic most frequently. Embolism from the vegetations is common. The valve cusps may be extensively ulcerated and perforated and even the *chordæ tendineæ* ruptured. These extensive lesions are caused by staphylococcus, streptococcus, pneumococcus, meningococcus, and gonococcus. Recovery from such disease is rare: the lesions heal with great scarring and deformity of the valves. The right side of the heart is involved in about 25 per cent. of the cases of acute bacterial endocarditis.

Subacute bacterial endocarditis due to the *Streptococcus viridans* and to the *influenza bacillus* is of different nature, the lesions being more discrete, less extensive and fulminating, and practically always involving the wall of the auricle or ventricle in addition to the valve cusps. Subacute bacterial endocarditis is almost always superimposed on abnormalities already caused by rheumatic endocarditis or congenital defect; it rarely attacks normal valves. The typical lesion is a vegetation, larger than in rheumatic but smaller than in acute bacterial endocarditis, consisting of bacteria and blood-platelets and fibrin invaded by round cells. The process extends by contiguity, apparently. Here again, embolism is common, and glomerular lesions in the kidneys with hematuria are frequent. The scars formed during recovery are quite similar to those of chronic rheumatic valvular disease, but are more extensive and involve the auricular and ventricular endocardium.

Arteriosclerotic valvular disease appears in middle and old age, often superimposed on chronic infectious or congenital valve lesions. It may occur in otherwise undamaged valves, the mitral and aortic being most commonly involved. At times the resulting calcification may bind one or both of the mitral cusps by solid brittle *chordæ tendineæ* to stony masses in the papillary muscles, and rocky projections may even protrude from a stenosed aortic valve into the lumen of the aorta. What percentage of the patients with sclerotic valve changes have previously had valvular disease we have no sure means of determining at the present time. Frequently only the ring of valve attachment is the site of calcification.

The Effect of the Valvular Disease.—The effect of chronic valvular

disease on the heart muscle and cardiac cavities is, of course, important. Aortic stenosis and also aortic regurgitation throw a great strain on the left ventricle and cause hypertrophy. *Aortic regurgitation* is much more important in this respect than is aortic stenosis; some of the very largest hearts ever recorded (800 to 900 and more grams) have been caused by it. The *cor bovinum* often indicates aortic regurgitation. Not only does the left ventricle hypertrophy when there is aortic regurgitation, but its cavity becomes enlarged (primary dilatation) to take care of the reflux of blood from the aorta during diastole. Apparently this dilatation and hypertrophy go hand in hand. *Aortic stenosis* may produce relatively little hypertrophy of the left ventricle and, if uncomplicated by aortic regurgitation, no primary left ventricular dilatation. Aortic regurgitation complicated by aortic stenosis is much less of a burden for the heart than aortic regurgitation alone.

Mitral stenosis throws a strain on the left auricle and right ventricle and therefore, when it is typical and well-marked, there is dilatation of the left auricle with thickening of its muscular wall, and hypertrophy of the right ventricle. Eventually even the right auricle may feel the burden, too, and respond with dilatation and hypertrophy. The left auricle being affected first may assume enormous proportions and cases are on record in which its bulk was larger than that of all the rest of the heart. The right ventricle may grow to equal the left ventricle in weight. The left ventricle is little affected.

Mitral regurgitation throws a strain chiefly on the left ventricle and left auricle, but eventually also on the right ventricle. The left ventricle tends to grow heavier and dilates in order to accommodate the extra blood which it takes in to compensate for the leak back into the auricle. It is often true that the heart is more enlarged by combined mitral regurgitation and stenosis than by mitral stenosis alone for this very reason. With slight degrees of mitral regurgitation, however, there is little change in the weight of the ventricles or in the size of their cavities.

Pulmonic stenosis is a great burden for the right ventricle and right auricle, and causes both to hypertrophy and dilate, often to a marked degree. Pulmonic regurgitation is very rare, but, of course, the strain, which is entirely on the right ventricle, produces dilatation and hypertrophy.

Tricuspid stenosis causes right auricular dilatation and hypertrophy, and, if marked, engorgement of liver and great veins. The ultimate strain is on the left ventricle. Tricuspid regurgitation affects right ventricle and right auricle.

Pathological changes in other organs are not due primarily to chronic valvular diseases of the heart, but rather to congestive failure (acute or chronic passive congestion) or to infectious processes (embolism). Pulmonary engorgement is, however, a common finding in mitral stenosis without demonstrable heart failure, and in such cases pulmonary "apoplexy" with a variable amount of hemoptysis is not rare. Pulmonary or cerebral infarction from embolism due to intracardiac thrombosis may be the first event to reveal the presence of chronic valvular disease (especially mitral stenosis).

Symptoms.—There are no symptoms characteristic of chronic valvular disease. Practically all the symptoms recorded in the text-books are those of heart failure or irritable heart: the fatigue pains of mitral stenosis or aortic regurgitation, anginal pain, dyspnea, palpitation (due to forceful heart action, premature beats, paroxysmal tachycardia, or auricular fibrilla-

tion), cough, weakness, and fainting. Even extensive damage of the valves, for example, well-marked aortic regurgitation, occasionally produces no symptoms at all. In such cases the myocardium is neither fatigued nor irritable. Therefore the clinical diagnosis of chronic valvular disease must depend on physical signs and the results of instrumental tests.

Signs of Chronic Valvular Disease Discovered by Physical Examination and Laboratory Tests.—In the discussion of the diagnosis of chronic valvular disease the valve lesions will be considered first individually and then collectively.

Mitral Valve Lesions.—Mitral valve damage is proved by an apical diastolic murmur, with or without a thrill, which begins a brief interval after the second heart sound, in the absence of an early diastolic murmur heard along the left border of the sternum.[1] There may or may not be a presystolic crescendo murmur at the end of it. This is probably the only positive evidence of mitral valve lesion that we possess. There are many signs that indicate the probability of mitral lesions but do not prove them. A very loud blowing or rough systolic murmur masking the first sound, heard best at the apex, and transmitted well to the axilla and perhaps to the back, is fair evidence of mitral damage with regurgitation, particularly if there is also a systolic thrill palpable at the apex, provided there are not present causes of cardiac dilatation to produce functional regurgitation, such as anemia, infection, or heart failure. In feeble old people without mitral valve damage there is occasionally a very loud systolic murmur at the apex which masks the first sound; this is sometimes associated with a calcified ring at the base of the valve. With a rheumatic history and some enlargement of the heart, a loud apical systolic murmur is practically pathognomonic of mitral damage with regurgitation, in the absence of pericarditis and acute rheumatic cardiac infection. If there is much cardiac enlargement, as in chronic nephritis with cardiac failure, such a murmur may result from functional regurgitation, though there is less likelihood of a thrill or of as much intensity of the murmur as goes with a valve lesion. At times this organic regurgitant murmur accompanies the diastolic murmur of mitral stenosis. Roentgenological evidence of a heart enlarged transversely with prominence in the region of the left auricle[2] is also good evidence of mitral valve disease. The electrocardiographic finding of pronounced abnormal right axis deviation with prominent auricular complexes (*P waves*) in Lead I or II is excellent evidence of mitral damage in the absence of pulmonic stenosis. Both of these changes come with advanced mitral stenosis, as a rule, and are corroborative evidence, the apical diastolic murmur proving the condition. Marked accentuation of the second sound at the second left interspace near the sternum (P_2 ++) is usual in chronic mitral disease. Auricular fibrillation existing in a young adult—under the age of forty years—almost always means rheumatic heart disease with mitral involvement, usually stenosis. There is, as a matter of fact, rarely organic mitral regurgitation without some stenosis, and also rarely mitral stenosis without some regurgitation. It is better to speak generally of mitral involvement, the high grades of which always mean mitral stenosis.

[1] Rarely a very large left ventricular cavity, as in chronic adhesive pericarditis, may give rise to the typical mitral diastolic murmur with normal mitral valve. This is probably to be accounted for, as may also be the Austin Flint murmur, by the abnormal change in the caliber of the blood-stream as it enters the ventricular cavity from the auricle.

[2] Probably this so-called enlargement in the region of the left auricle is really due to increase in size of the right ventricle, especially the infundibulum.

Other signs that suggest the possibility of mitral disease are the sharp first sound at the apex, with or without a very brief thrill in a heart not beating violently. This short, so-called presystolic murmur and thrill may be found in nervous, overactive hearts as well as in mitral stenosis. A reduplication of the first sound at the apex, and a prominence of the third heart sound should also cause suspicion of mitral stenosis. These findings and the sharpness of the apical first sound indicate the need of exercise (or amyl nitrite inhalation) to increase the speed and force of the heart to bring out the mitral diastolic murmur, with or without its presystolic accentuation, in early or slight grades of mitral stenosis. Recently a very loud third heart sound close to the sternum in the fourth space has attracted attention, the mitral diastolic murmur being found at the apex immediately following the third heart sound in several such cases. A pronounced presystolic murmur alone without the mid-diastolic murmur is rarely heard, and unless the presystolic murmur is quite definite it should not be interpreted as meaning mitral stenosis. Moreover, it should be remembered that when auricular fibrillation sets in, the auricles cease co-ordinate action, so that the presystolic phase of the diastolic murmur of mitral stenosis disappears and leaves the telltale mid-diastolic murmur behind. Since auricular fibrillation is a very common condition, especially in hearts with mitral stenosis, this is a very important point to remember.[1] It shows the greater need of relying on the diastolic rather than on the presystolic murmur in the diagnosis of mitral stenosis. Mackenzie said, "In the very early stages—some years before the appearance of a murmur—I have detected a slight presystolic thrill. The first murmur to appear precedes or runs up to, and seems to terminate in the first sound, and is audible over a small area around the apex." It is unsafe, however, to interpret such a slight "presystolic" thrill as early mitral stenosis.

The diastolic murmur already so frequently mentioned is of a characteristic type. It begins an appreciable interval after the second sound and at once after the third sound when that is audible; it is often *diminuendo* in character—low pitched and rumbling if the heart rate is slow. It is best heard with the patient recumbent and by the use of the bell stethoscope. The murmur is usually localized at or just inside the maximal apex impulse. It is accentuated by exercise. With well-marked aortic regurgitation the apical diastolic murmur, with or without presystolic accentuation, may mean simply the so-called functional mitral stenosis described by Austin Flint.[2] Aortic regurgitation with a mitral diastolic mur-

[1] Gerhardt (Herzklappenfehler, Vienna and Leipzig, 1913) and others claim that an important factor in the production of the presystolic murmur of mitral stenosis is the increasing stenosis in each heart cycle when ventricular systole begins just preceding the actual closure of the mitral valve and the first sound of the heart. If the rate is rapid so that there is still a good-sized stream of blood entering the left ventricle from the left auricle when the ventricle begins to contract, the increasing narrowness of the stiffened mitral valve may conceivably contribute largely to the *crescendo* quality of the presystolic murmur. This particular *crescendo* quality may not be produced by the auricular contraction, although the general accentuation of the diastolic murmur in presystole is so accounted for. The reported finding of occasional *crescendo* accentuation of the diastolic murmur just preceding the first sound in auricular fibrillation, when the diastolic interval is short, may be explained as outlined above; but certainly the chief cause for the presystolic (though perhaps not *crescendo*) accentuation of the mitral diastolic murmur is auricular contraction.

[2] A more likely cause for the Austin Flint murmur than narrowing of the mitral valve by pressure from the regurgitant stream on the aortic cusp of the mitral valve is the effect of left ventricular dilatation (always found in chronic aortic regurgitation) on the caliber of the stream of blood entering from the auricle through the normal mitral valve.

mur in a rheumatic heart should generally be considered as a combination of aortic regurgitation and organic mitral stenosis; in a syphilitic heart, as aortic regurgitation and "functional mitral stenosis." Thayer, in 1901, reported a mitral diastolic murmur in 45 out of 74 cases of aortic regurgitation which came to necropsy at the Johns Hopkins Hospital. There was stenosis or other abnormality of the mitral valve in 28 of these 74 cases, so that by subtracting this number from the total figure we have a probable ratio of 17 : 46, or less than half of the pure aortic regurgitation cases exhibiting the Austin Flint murmur. In several recent cases of marked aortic regurgitation—syphilitic in origin—examined by the writer, this murmur has been lacking.

Other conditions suggesting the possibility of mitral valve damage are the history of rheumatic fever, especially if repeated attacks have occurred; cerebral embolism (from left auricular thrombosis) in a young person, generally of the female sex; hemoptysis in a young person without tuberculosis; left recurrent laryngeal nerve paralysis; and the mitral facies with pulmonary congestion in various stages of heart failure. The pulse is often stated to be small and the systolic pressure low in mitral stenosis; this is not infrequently so in cases of auricular fibrillation, but it is certainly not always the case.

Tricuspid Valve Lesions.—Damage to the tricuspid valve is relatively rare, and is usually difficult to diagnose. The frequency of functional tricuspid regurgitation is great as compared with organic changes in the valve which produce regurgitation or stenosis. Marked tricuspid stenosis is manifested by a mid-diastolic murmur with or without a presystolic phase which is localized over the lower half of the sternum, or just to the left of it. But care must be taken to avoid confusion with a widely heard mitral diastolic murmur, or the early diastolic murmur of aortic regurgitation which is heard in the same place and also higher. Mackenzie states that he has heard the tricuspid presystolic murmur only three times. Possibly this is because in most cases it is likely to be associated with auricular fibrillation. Tricuspid stenosis is found in advanced rheumatic heart disease rarely without mitral stenosis. Osler and Gibson state that in a group of 173 cases of tricuspid stenosis, this lesion occurred alone in only12; it was associated with a mitral lesion in 97; with mitral and aortic lesions in 58; with mitral and pulmonic in 3; and with pulmonic stenosis in 3.

There are other signs suggestive of organic tricuspid disease. A large liver may be present; although Osler and Gibson say that it is not always enlarged with tricuspid stenosis. Mackenzie looked upon "pulsation of the liver with a marked wave due to the auricle as an evidence of possible tricuspid stenosis." But, of course, the auricles may fibrillate and the auricular wave disappear. Levine states that he has recently seen 3 cases of tricuspid stenosis proved at necropsy, two of them diagnosed *ante mortem*, all with auricular fibrillation and mitral stenosis. One of the striking features of these cases was the enlarged non-pulsating liver without evidence either of cardiac failure or of alcoholic cirrhosis. But in such cases one must look out for chronic mediastino-pericarditis. Also, chronic mitral stenosis alone may produce chronic enlargement of the liver.

Cyanosis, marked in some cases and with a jaundiced tinge to the skin, polycythemia (even 8 or 9 million red cells per c.mm.), dilated cervical veins, increased dulness to percussion to the right of the sternum, particu-

larly in the third and fourth interspaces, and a rather high abnormal prominence of the right auricular shadow by Roentgen ray, are all said to support the diagnosis of tricuspid valve disease. A fairly marked stenosis is necessary to bring out some of these findings, but a superficial, high-pitched, long, rough systolic murmur maximal over the sternum at about the level of the fourth interspace and to the left rather than to the right, accompanied by a thrill, suggests organic tricuspid regurgitation or interventricular septal defect. The heart is enlarged transversely in tricuspid disease. Electrocardiograms have shown abnormal right axis deviation, partly at least because mitral stenosis is almost always associated. Also in the absence of auricular fibrillation the auricular complex (*P wave*) is increased in size. The venous blood-pressure is increased. Except for the frequency of auricular fibrillation the arterial pulse is not abnormal.

Aortic Valve Lesions.—A diastolic murmur beginning early and best heard down the left border of the sternum, associated with the water-hammer pulse, is pathognomonic of aortic regurgitation. This murmur may also be heard along the left border of the heart and at the apex, but it should not be confused with the mitral diastolic murmur at the apex, which is later in time and more rumbling in character. Whether or not the cusp or cusps involved have anything to do with the variable transmission of the murmur is not known. A musical diastolic murmur suddenly appearing after trauma or exertion usually means a valve rupture.

The marked water-hammer quality of the pulse described by Corrigan is also pathognomonic of aortic regurgitation, although a full pulse and capillary pulsation occur in other conditions as well. Various suggestive phenomena, such as the pistol shot heard over the great arteries as in the groin, the to-and-fro murmur on pressure over the great vessels (Duroziez's sign), and the visible pulsation or throbbing of the arteries of the head and extremities, are dependent on the markedly increased pulse pressure due chiefly to the very low diastolic blood-pressure. This wide pulse pressure with very low diastolic reading is practically pathognomonic of aortic regurgitation. The symptoms of ringing in the ears and vertigo sometimes complained of by patients with aortic regurgitation probably have their origin in the water-hammer type of pulse. An interesting phenomenon observed by Hill and Rowlands in aortic regurgitation is the much higher systolic pressure in the femoral artery than in the brachial artery. A patient in the Massachusetts General Hospital with marked aortic regurgitation showed a brachial systolic blood-pressure of from 132 to 136 mm. of Hg., and a femoral systolic blood-pressure of 270 mm. The diastolic pressure was not clearly determinable in either artery, but apparently lay between 10 and 20 mm. This preponderance of femoral pressure may be due to an arterial tonus maintained to support properly the cerebral circulation.

Absence or weakness of the aortic second sound may be found in aortic regurgitation, but much less often than in aortic stenosis. The heart is always enlarged if there is much regurgitation, and it is when regurgitation is marked that a very large heart (*cor bovinum*) may be found. The apex impulse is often in the sixth or seventh space and out close to the anterior axillary line. The Roentgen ray discloses a large heart increased in size downward and to the left with a rounded apex. Increased excursion of the pulsation of the aortic arch is common in aortic regurgitation. The aortic shadow is increased in size if there is associated a syphilitic aortitis.

In uncomplicated cases the electrocardiogram reveals markedly abnormal left axis deviation, the most marked observed. Krehl, however, has shown that slight aortic regurgitation may occur without any obvious enlargement of the heart.

Functional regurgitation through the aortic valve was described by Corrigan and has been spoken of since by others, but it is rare.

Confusion of aortic with pulmonic regurgitation should be avoided by the rarity of the latter and by failure to find signs of increased pulse pressure in pulmonic regurgitation. A diastolic murmur heard over the sternum has been recorded as of venous origin, and has been encountered in exophthalmic goiter; but such cases should present but little difficulty. Recently, in a case previously diagnosed as slight aortic regurgitation because of the finding of an early diastolic murmur heard along the left border of the sternum, from the second intercostal space downward, the Roentgen ray showed marked prominence in the region of the pulmonary artery, with marked pulsation in the region of the hilum of the right lung. The roentgenological diagnosis of the condition was "probable patent *ductus arteriosus*," according to Groedel. The electrocardiogram revealed marked preponderance of the right ventricle, certainly not supporting aortic regurgitation. The patient was a young woman, without a history of rheumatic fever, in whom some cardiac symptoms had developed following influenza one year before. There was no water-hammer quality to the pulse and no systolic murmur at the base of the heart. The diagnosis must rest in doubt, though a very rare pulmonic regurgitation of unknown cause would best explain all the signs.

It must be added finally that a slight degree of aortic regurgitation is common and is not associated with any pulse or blood-pressure changes. If diagnosis is not made until these appear, it is probable that at least 50 per cent. of all cases of aortic regurgitation will be missed. The diagnosis must be made from the murmur; confusion with possible pulmonic regurgitation should not deter one, since the latter disease is very rare.

Aortic stenosis may be definitely diagnosed, in the absence of signs of an aneurysm, on the discovery of a rough systolic murmur with a systolic thrill over the aortic area to the right of the sternum in the second interspace and transmitted to the vessels of the neck. Stokes noted that this murmur at times may be audible at some distance from the chest wall. The pulse is generally small and anacrotic, or plateau-like, or both, a very important confirmatory finding. Also the bisferiens pulse has been recorded in aortic stenosis. The blood-pressure is not remarkable, as a rule, except for a low pulse pressure[1]; if there is considerable regurgitation so that the stenotic effect is overbalanced, there may be an increased pulse pressure and absence of the anacrotic and plateau pulse characteristics. The heart is usually enlarged downward and to the left, as shown by palpation, percussion, and the Roentgen ray, but never to the degree found in uncomplicated aortic regurgitation. In aortic stenosis the aortic second sound is usually absent or much diminished. The electrocardiogram may show abnormal left axis deviation. Mitral stenosis may be associated with aortic stenosis and thus may neutralize the abnormal left axis deviation.

Slight degrees of aortic stenosis may be suspected when there is rheumatic heart disease with aortic regurgitation and a blowing systolic murmur at the aortic area transmitted to the neck, but without great loudness or a

[1] It is, however, of considerable interest that an "auscultatory gap" is not rarely found in the process of blood-pressure estimation in aortic stenosis.

thrill. Aortic stenosis is frequently diagnosed, however, when it does not exist, various other conditions being common causes of the systolic murmurs at the aortic area. Aneurysm and aortic dilatation may be confused with aortic stenosis of slight or moderate degree. Pulmonic stenosis should not be confused because its systolic murmur, though also loud and accompanied by a thrill, is heard best to the left of the sternum and is not transmitted to the neck, and cyanosis is usually present.

Pulmonic Valve Lesions.—Chronic valvular disease involving the pulmonic valve is very rare. Endocarditis of the pulmonic valve is almost invariably associated with mitral, aortic, or tricuspid lesions alone or combined. Pulmonic regurgitation may be suspected by the finding of a murmur beginning early in diastole with or immediately following the second sound and extending down the left border of the sternum in the absence of the water-hammer pulse and in the presence of marked chronic mitral stenosis and pulmonary congestion; but the murmur of a slight degree of regurgitation through the pulmonic valve may be indistinguishable from that of slight aortic regurgitation, since the position and character of the murmurs are identical, and in view of the small amount of aortic regurgitation there may be no water-hammer character to the pulse. In such cases roentgenographic and electrocardiographic evidence should be helpful in indicating which ventricle shows the greater hypertrophy. Organic pulmonic regurgitation may not be distinguishable from functional pulmonic regurgitation. The functional type occurs in cases of advanced mitral disease with much pulmonary engorgement. The murmur of functional pulmonic regurgitation—due to the stretching of the pulmonic ring—is that described by Graham Steell. Its frequency is a matter of some discussion. It is said to appear and disappear with changes in the condition of the patient. It may be difficult to distinguish from slight functional aortic regurgitation. I feel very doubtful about calling a slight early diastolic murmur heard along the left border of the sternum a Graham Steell murmur. Graham Steell himself found the pulmonic regurgitant murmur rarely. Osler and Gibson say: "From the clinical standpoint, so much that has been said about pulmonary regurgitation is either unproved or as yet incapable of proof that the subject should be approached with the greatest caution. . . . Pulmonary regurgitation is more often diagnosed than existent. In several cases in which we thought it to be present in young persons the lesion proved to be aortic." The rarity of pulmonic regurgitation should cause long hesitation before the diagnosis is made.

Pulmonic stenosis is a fairly common congenital heart abnormality, but as the result of disease after birth is exceedingly rare. A loud systolic murmur in the second interspace to the left of the sternum with a systolic thrill, and not transmitted to the vessels of the neck, is pathognomonic of pulmonic stenosis in the absence of signs of an aneurysm or a plateau radial pulse. Two types of congenital stenosis are described: that occurring low and involving the infundibulum of the right ventricle, and that involving the valve itself. The former variety is said to show the maximal murmur and thrill in the third left interspace, and the latter in the second left space. With any pronounced degree of stenosis there is considerable cyanosis, partly as the result of cardiac insufficiency, but still more as the result of the right to left shunt of venous blood through defective auricular or ventricular septum. An interventricular foramen is found in a large number of the cases

of pulmonic stenosis. Polycythemia and clubbing of the fingers may occur. Enlargement of the heart to the left with the apex tilted up is shown by the Roentgen ray. Vaquez and Bordet call this the "wooden shoe" (*sabot*) shape. Also the Roentgen ray shows prominence in the region of the pulmonic artery. The electrocardiogram indicates abnormal right axis deviation, and it is in these cases of congenital pulmonic stenosis that the highest grades of right axis deviation are found. Stenosis of the pulmonic valve acquired after birth should be distinguishable from the congenital type by the history of the case and by the evidence of other endocarditic lesions.

Combined Valve Lesions.—The combination of valve lesions causes a combination or a neutralization of the signs of the individual valve changes. For example, stenosis of the aortic valve cuts down and may completely neutralize the Corrigan pulse of aortic regurgitation. Aortic regurgitation balances the right ventricular hypertrophy of mitral stenosis so that the whole heart may be symmetrically enlarged. The characteristic murmurs of both lesions will be present in such a heart, the early diastolic murmur of aortic regurgitation along the left border of the sternum and the later rumbling diastolic murmur of mitral stenosis at the apex. Sometimes an apparent difficulty may arise as to whether these murmurs represent the diastolic murmur of true mitral stenosis with the functional pulmonic regurgitant murmur of Graham Steell, or the diastolic murmur of aortic regurgitation with the functional mitral diastolic murmur of Austin Flint. Other data, such as the type of ventricular enlargement (left or right sided) determined by electrocardiogram and Roentgen ray, and the presence or absence of the Corrigan pulse or of pulmonary congestion, should clear up such doubts quickly. Probably in rheumatic heart disease these two diastolic murmurs most often mean that there is both organic aortic regurgitation and organic mitral stenosis. More likelihood of error arises when one attempts to diagnose damage to three valves. Osler and Gibson write:

> As a rule the physician is in a safer position if he limits his diagnostic ambition to two valves. Clinically, when lesions of three or four valves are determined with accuracy, mortifying *postmortem* disclosures are not unlikely to follow.

Complications.—The most common complications of chronic valvular disease are heart failure of the congestive type, and irritability of the heart as shown by palpitation and arhythmia. In the past, most accounts of the symptoms, signs, and treatment of chronic valvular disease have consisted largely in a recital of the evidence and treatment of heart failure. In the case of aortic valve lesions the strain is chiefly on the left ventricle, and it is that ventricle which tends first to produce such signs and symptoms of failure as edema of the legs and Cheyne-Stokes respiration. Mitral stenosis exhausts the right ventricle first with the early appearance of cyanosis and pulmonary edema. Pulmonic stenosis is also a cause for right ventricular failure. The three valve lesions of aortic regurgitation, mitral stenosis, and pulmonic stenosis are the most serious of the burdens imposed on the myocardium by chronic valvular disease. Even the strongest heart muscle must become exhausted eventually by such a strain, but often in these hearts the muscle is itself diseased and so unable to carry the burden long without trouble. Neither the old view that the valve disease is the chief factor in the production of heart failure nor the modern

view that weak muscle is the chief cause is sufficient. Both factors play their part inseparably, though the strain due to the valve deformity is probably the more important factor.

Irritability of the heart is common in chronic valvular disease. Forceful uncomfortable heart beats in aortic regurgitation particularly, paroxysmal tachycardia, auricular flutter, and auricular fibrillation (paroxysmal or permanent) especially in mitral stenosis, and premature beats and effort syndrome with any lesions, are frequently found, but are not essential accompaniments of chronic valvular disease.

Embolism is a complication which is particularly apt to accompany mitral stenosis. Hemiplegia, often transient, in young people may result from cerebral embolism from left auricular thrombosis in mitral stenosis. Usually, however, embolism of cardiac origin results from infectious thrombi in acute or subacute bacterial endocarditis.

Laryngeal paralysis with consequent hoarseness, which is sometimes found in marked mitral stenosis, is the result of pressure of the left recurrent laryngeal nerve against the aorta by the pulmonary artery, which is in its turn displaced by the much enlarged left auricle or right ventricle.

Clubbing of the fingers is found in congenital pulmonic stenosis and in subacute bacterial endocarditis, but not in ordinary chronic valvular disease.

One of the most serious complications of chronic valvular disease of congenital or rheumatic origin is the superimposed subacute bacterial endocarditis which is usually fatal.

Differential Diagnosis.—The commonest and most important conditions with which chronic valvular disease may be confused are those giving rise to the so-called functional heart murmurs.

A *functional systolic murmur maximal at the apex* may be heard when there is a dilatation of the mitral valve ring with failure of the mitral cusps to close the aperture completely; this may accompany cardiac dilatation, as in primary heart failure; or it may accompany adhesive pericarditis, severe anemia, or severe infectious diseases. Sometimes a functional systolic murmur is heard at the apex without known cause, even in normal individuals. In some of these cases probably the mitral valve is not perfect and fails to close completely. The functional systolic murmur at the apex is generally less intense than the organic systolic murmur, but undoubtedly slight murmurs do occur with organic mitral regurgitation of lesser degree. A very loud blowing systolic murmur at the apex masking the first sound is much more likely to be evidence of organic than of functional mitral regurgitation unless the heart is large and dilated. The smaller the heart, the more likely it is that the *very loud* systolic mitral murmur is organic. Transmission of the apical systolic murmur to the axilla and elsewhere depends on the intensity of the murmur, whether organic or functional. Organic murmurs are more often transmitted because they tend to be louder. An excellent discussion of systolic cardiac murmurs was published by Thayer in 1925.

A *functional systolic murmur maximal over the base of the heart just to the left of the sternum in the second intercostal space—the so-called pulmonic area*—is the commonest heart murmur of all. It is heard in at least 50 per cent. of all individuals in the recumbent position, much less commonly in the erect position. It seems to be a normal phenomenon, but its cause is not known. It is exaggerated in full expiration, and the mechanism of its pro-

duction may be related to that which normally causes reduplication of the pulmonic second sound in full expiration—an increase in pressure in the pulmonary circulation which perhaps causes dilatation of the pulmonary artery; or there may be compression or kinking of the pulmonary arteries with resultant murmur. The functional pulmonic systolic murmur is rarely if ever accompanied by a thrill, probably on account of its low intensity. Any circulatory weakness—particularly severe anemia—tends to produce loud functional pulmonic systolic murmurs. Congenital cardiac defects such as pulmonic stenosis, patent *ductus arteriosus,* and interventricular septal defect are to be differentiated from the functional pulmonic systolic murmur. In the case of the congenital heart defects the murmur is apt to be very intense and accompanied by a systolic thrill; while, in addition, with pulmonic stenosis there is generally cyanosis from birth; with patent *ductus arteriosus,* a long diastolic murmur is also usually heard along the left border of the sternum; and with interventricular septal defect the maximal murmur is low in position, generally at the fourth left costal cartilage close to the sternum. Pulmonic stenosis acquired after birth is very rare, but would be indistinguishable from uncomplicated congenital pulmonic stenosis if of similar degree.

A functional systolic murmur maximal over the base of the heart just to the right of the sternum in the second intercostal space—the so-called aortic area—is quite common, and may be heard most often when the aorta is dilated. It does not come from roughening but from change in the caliber of the blood-stream as it leaves the aortic valve and enters the dilated aorta. Such dilatation of the aorta develops particularly in syphilitic aortitis, aortic arteriosclerosis, and aortic dilatation in patients with hypertension. It may not have obvious cause, but it is rarely found in normal people. While aortic stenosis may occur without a systolic thrill or change in pulse pressure and shape, it is unwise to base this diagnosis on the murmur alone. Functional "aortic" systolic murmurs do not produce thrills.

A functional tricuspid systolic murmur should be found at the lower end of the sternum, but may be masked by the functional mitral systolic murmur when there is dilatation of both mitral and tricuspid rings. A functional tricuspid systolic murmur is not as frequent as a functional mitral systolic murmur, although functional tricuspid regurgitation is common. Probably the relatively low pressure in the right side of the heart accounts for the less frequent occurrence of functional systolic murmurs at the lower end of the sternum.

A functional diastolic murmur maximal at the apex is infrequently found. It resembles the mitral stenotic diastolic murmur exactly in time, character, and position, but is, as a rule, less intense and is not often accompanied by a thrill. In well-marked aortic regurgitation it is called the Austin Flint murmur and it has been thought to be due to a functional mitral stenosis resulting from the partial closing of the mitral valve during diastole by the regurgitant stream of blood from the aortic valve impinging on the anterior cusp of the mitral valve. But since exactly the same murmur is found now and then with left ventricular dilatation due to adherent pericardium or to hypertension with failure, or perhaps to severe anemia, it is likely that the mechanism of its production is the same. Some patients with aortic regurgitation show the most marked dilatation of the left ventricular cavity known. An unusual change in the caliber of the blood-stream entering a dilated left

ventricle from a normal mitral valve may account for this well-known functional apical diastolic murmur.[1]

A functional diastolic murmur which is heard best along the left border of the sternum and less well at either the "aortic" or "pulmonic" area, may be due to either functional pulmonic regurgitation (Graham Steell murmur) or functional aortic regurgitation. Both are very rare conditions and it is almost always wiser to regard an early diastolic murmur which is maximal along the left border of the sternum as evidence of organic aortic regurgitation. The functional murmur is nearly always slight and is, therefore, not associated with much change of blood-pressure, but in character, time, and position it is indistinguishable from the organic murmur. The functional pulmonic regurgitant murmur occurs in marked mitral stenosis with increased pressure in the pulmonary circulation, and consequently with abnormal pressure in diastole against the pulmonic valve, the ring of which may itself be weak. The functional aortic regurgitant murmur may be found in patients with systemic hypertension and weakness of the aortic valve ring, or, in rare cases, the latter cause alone may be responsible. An important feature of the functional diastolic murmurs at the base of the heart is that they tend to be transient, appearing and disappearing with changes in the patient's condition.

A functional tricuspid diastolic murmur has not been recorded.

Other conditions to be differentiated from chronic valvular disease are *aortic aneurysm, patent ductus arteriosus, interventricular septal defect, other rarer congenital defects such as coarctation of the aorta,* and *pericardial friction rubs.* An aortic aneurysm of the ascending or descending aorta may simulate to some extent aortic or pulmonic stenosis, but the etiology, the more marked thrills of valvular stenosis, the occasional finding of unequal pulses with aneurysm, the increased dulness at the base of the heart, both by percussion and by *x*-ray, the occasional visible basal tumor or pulsation, and the positive Wassermann reaction and vigorous arterial pulse in the neck with aneurysm help to differentiate the conditions. The congenital cardiac defects mentioned above can usually be differentiated from chronic valvular disease by the history and by the unusual position and character of the murmurs. Pericardial friction rubs are usually easily distinguished from the murmurs of chronic valvular disease by their scratchy, near-to-the-ear character, by their brief duration (rarely more than a few days), and by the frequency of pericardial effusion coincident or following.

Prognosis.—Pure organic *mitral regurgitation* of rheumatic origin, if not of marked degree, has a good prognosis. Without further rheumatic infection or progressive deformity of the valve with ensuing stenosis, and without the complication later in life of acute or subacute bacterial endocarditis, the patient should live in full activity for practically the normal span of life.

Mitral stenosis, almost invariably rheumatic in origin, is a very common condition in some parts of the world, as in New England, and it varies considerably in prognosis. The forecast may be said to be almost always unfavorable. The lesser degrees, which were once usually called mitral regurgitation, may shorten life only a little or not at all; but marked mitral stenosis is very serious. It handicaps activity and is often fatal before or soon after the patient reaches adult life. The strain on the heart is appar-

[1] Heart murmurs are produced by marked changes in the caliber of the blood-stream as it passes through the heart, either forward or backward.

ently very great, no matter what the condition of the muscle. Auricular fibrillation and congestive failure lead to death as a rule, but now and then subacute (or acute) bacterial endocarditis, or an intercurrent infection, is the cause of death.

Often the question comes up as to whether or not mitral stenosis or other chronic valvular lesions should be a bar to *pregnancy*. As there is no rule on which to base such a decision each case must be determined on its merits. There is usually little difficulty during pregnancy and childbirth, unless the stenosis is marked or auricular fibrillation is present. Both of these conditions—*i. e.*, very marked mitral stenosis and auricular fibrillation—contraindicate pregnancy. Auricular fibrillation especially is a very serious complication.

Almost the same may be said of *rheumatic aortic regurgitation* of slight extent as of rheumatic mitral regurgitation. The higher degrees of aortic regurgitation are, however, a great strain on the heart. The victim usually does not attain and rarely survives middle age. Death is caused by heart failure or by acute or subacute bacterial endocarditis in youth.

Syphilitic aortic regurgitation is always a serious sign—generally of advanced cardiovascular syphilis. Patients with this disturbance rarely survive for more than a few years at the very outside. Death often comes from rapidly progressive failure six to twelve months after the discovery of the lesions, but in exceptional cases may be delayed much longer.

Arteriosclerotic aortic regurgitation is but part of a general advanced arteriosclerosis which usually leads to death within a few years. It of course adds a further burden to an arteriosclerotic heart.

Rheumatic aortic stenosis has a much better prognosis than a similar grade of aortic regurgitation, and may allow survival to old age. The presence of aortic stenosis improves the prognosis of aortic regurgitation. Aortic stenosis of arteriosclerotic or syphilitic origin is rare, and its prognosis is similar to that of aortic regurgitation of the same etiology.

Tricuspid valvular disease is practically always complicated by disease of either the mitral or aortic valve, or both, and its prognosis depends on that of the other valvular defects, except when tricuspid stenosis is marked and adds to the gravity of the situation.

Pulmonic valvular disease is a serious condition, whether congenital or acquired. By far the most common lesion of this type is congenital pulmonic stenosis. This condition, even though "compensated for" by some other defect like patency of the *ductus arteriosus* or interventricular septal defect, is generally fatal early in life, but may rarely allow survival to youth or even to middle age. It handicaps activity very much and patients who do not succumb to acute infectious disease in childhood die of heart failure or subacute bacterial endocarditis in early adult life.

Chronic valvular disease is thus a serious handicap and almost always limits both the duration and activity of life. Death comes generally because of primary heart failure, but may result from the complication of acute or subacute bacterial endocarditis or other acute infectious disease against which the resistance is lowered.

Treatment.—Very little need be said about the treatment of chronic valvular disease. We are not concerned here with the treatment of its complications (such as heart failure, either congestive or anginal) or of cardiac irritability represented by the arhythmias.

The treatment of chronic valvular disease itself must be surgical. An attempt has been made to cut and thus to enlarge the stenosed mitral valve by *operation*, but this method of treatment is still in the experimental phase. Only once or twice has such an operation been successful or even been followed by survival; the mortality in a small group has been very high. Perhaps the production of an interauricular foramen surgically would be more successful. No operative attempt has yet been made to correct the valve defects in the other more serious conditions—aortic regurgitation and pulmonic stenosis.

There is no *drug therapy* yet devised to improve the condition of the scarred valves. Only in the progressive changes in the aortic valve which are due to syphilis is there hope from drugs at present. Even in cardiovascular lues, however, the antisyphilitic treatment may afford little benefit, and sometimes in large dosage may do harm and lead to early death. It should, however, be attempted.

Of course the prevention of further infections which are apt to damage the valves is of prime importance in individuals with chronic valvular disease. Tonsillectomy, avoidance of exposure to cold and wet, and early use of salicylates in rheumatic fever are worth while. Moving one's residence from an unfavorable (cold and wet) to a favorable (warm and dry) climate is probably generally helpful.

Of the greatest importance of all is the campaign now under way to prevent the factors which produce chronic valvular disease. The wiping out of rheumatic fever and chorea, scarlet fever, syphilis, acute and subacute bacterial endocarditis, and presenile arteriosclerosis is more important than the discovery of surgical or other methods of treatment.

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TREATMENT OF CARDIAC FAILURE

Prophylaxis.—Preventive measures are becoming increasingly important in the treatment of heart failure. Their effectiveness varies greatly, but, as a rule, is more or less proportional to the promptness with which they are begun and the thoroughness and intelligence with which they are

carried out. Prophylaxis is designed to control conditions liable to cause further damage to the diseased heart; protect the heart against overtaxation; and increase the cardiac efficiency.

Control of Deleterious Conditions.—Careful search should be made for all evidences of general or focal infection. Every such condition must be eradicated if possible. Chronic intoxication should be eliminated; the use of alcohol interdicted; overindulgence in coffee, tea, and tobacco checked; and intoxication from the digestive tract controlled by appropriate therapy and regulation of diet. Finally, general hygienic measures are to be adopted in order to avoid acute infections.

Protection of the Heart Against Overtaxation.—The normal, large reserve power of the heart is more or less constantly employed by the diseased heart to meet the needs of the body even when at rest. Consequently in cardiac disease there is a diminished reserve with which to meet any added demands. If this be small, signs of heart failure follow very moderate exertion; when there is no longer any reserve, failure is present even during rest. Although the diseased heart may be overtaxed many times and recover, the degree of efficiency which preceded the attack of failure is probably never quite regained. For this reason, the discovery of cardiac abnormality should at once lead to the adoption of measures to prevent overstrain.

Physical and mental exertion, worry, anxiety, anger, and haste, as well as dietetic indiscretions, overindulgence in food, and the lack of sleep and rest are all potent factors in overtaxing an impaired heart. Painstaking, detailed investigation of every phase of the patient's daily life is therefore essential for proper treatment. Surgical operations should be avoided, but if this is impossible the patient should be properly prepared in advance by rest and often by partial digitalization. The operation should be made as brief and simple as conditions permit. Ether is the most desirable general anesthetic. Convalescence should be prolonged sufficiently to insure maximal cardiac recovery. Married women of childbearing age should be discouraged from becoming pregnant. If pregnancy occurs the patient must be watched carefully, but usually may be allowed to go to term. Labor preferably should not be induced, but the second stage may be curtailed as much as possible by the use of forceps.

Increase in Cardiac Efficiency.—To increase the cardiac efficiency the general nutrition must be made as good as possible by regulation of the diet and the elimination, and by the establishment of suitable, general hygiene. Massage, passive and resistance movement, and hydrotherapy help maintain and develop the muscular efficiency of the heart as well as that of the body as a whole. When conditions permit, a careful graded course of exercises should be prescribed, under the constant observation of the physician. This prevents too rapid or too great increase in the amount of physical exercise. If the heart is not too seriously affected, and auricular fibrillation is absent, the cardiac efficiency may often be surprisingly increased for long periods of time.

Restorative Treatment.—After symptoms of failure have arisen, treatment must be directed to the prompt restoration of cardiac efficiency. Its nature depends chiefly on the degree of failure, although the details are somewhat influenced by the type of failure. At the beginning of heart failure a few days' rest in bed is often necessary, although many patients can safely

be up and about. The essentials of treatment are rest for the heart and elimination of cardiac strain. These are provided by adoption of general prophylactic measures, and by controlling symptoms with drugs. Dyspnea, exhaustion, and the other early signs of congestive failure are best controlled by oral administration of digitalis. The dose for an adult should be from 1 to 2 or 2.5 c.c. (ɱxv–xl) of a standardized tincture four times a day; or the equivalent in the form of the powdered leaf (0.1 to 0.25 gm.—gr. jss–iv). With this dosage from four days to one week are needed to digitalize the patient. Thereafter, administration of digitalis should be stopped. Smaller doses are of little use except to continue the digitalization already induced.

Attacks of heart pain are sometimes relieved almost at once by inhalation of amyl nitrite. The usual dose is from 0.2 to 0.3 c.c. (ɱiij–v). This is enclosed in small glass pearls which can be carried easily and broken into a handkerchief when needed. Nitroglycerin is equally efficacious and acts nearly as rapidly. It can be carried in the form of tablet triturates, one or more of which should be allowed to dissolve beneath the tongue. The average dose is from 0.5 to 1.0 mgm. (gr. $\frac{1}{100}$–$\frac{1}{50}$). The tablets should be reasonably fresh and should be kept in a tightly corked vial. When the pain is severe, or when it does not yield to the nitrites, hypodermic injection of morphin (8 to 15 mgm.—gr. $\frac{1}{8}$–$\frac{1}{4}$) may be necessary. Morphin is required also to control the severe paroxysmal dyspnea.

Contrary to the statements of Mackenzie, digitalis is not infrequently valuable in heart pain to relieve the heart failure which may be largely responsible for the pain. This drug should at least be tried if attacks of pain recur frequently as the result of cardiac exhaustion. Its intermittent use at times prevents further recurrences for months and even for a year or more.

The use of mild sedatives is valuable at the onset of failure to allay nervousness and anxiety and to insure adequate sleep. The bromids are the most satisfactory as they do not depress the heart. Hydrated chloral and such hypnotics as barbital (veronal) and luminal may be given to relieve sleeplessness. They should be employed cautiously, in doses just large enough to promote normal sleep.

The restoration of normal rhythm by quinidin is sometimes followed by complete recovery of cardiac efficiency in the early cases with auricular fibrillation. Quinidin is best administered orally in capsules. A dose of 0.4 gm. (gr. vj) should be given four times during the day and once of night. If there are no such ill effects as signs of cinchonism, increase of the ventricular rate to 160 or over, or respiratory symptoms, this medication may be continued for three or four days. If sinus rhythm is not restored the dose may then be increased to a maximum of 0.8 gm. (gr. xij) five times daily. This may be continued for three days: thereafter it should be discontinued if fibrillation persists. When sinus rhythm is restored it may continue for months without further administration of quinidin. If fibrillation returns quinidin may again check it and keep it in check when a daily dose of between 0.4 and 0.8 gm. is taken. This is commonly spoken of as *rationing*. Quinidin should not be administered without full knowledge of its dangers and limitations.

Advanced heart failure necessitates the enforcement of complete mental and physical rest. The patient should be confined to bed and comfortably

supported in a semirecumbent position if he is orthopneic. The diet must be light, bland, and easily digestible. The presence of edema requires restriction of the fluid intake to 1500 c.c. (3 pints), or less, in twenty-four hours. When edema is great either a "salt-free" diet with restricted fluids, or the Karrel diet (800 c.c. of milk per day) may be desirable for about a week. One or two small doses of morphin (8 to 15 mgm.) may be required at the outset to relieve the patient's anxiety or to control severe breathlessness. Sedatives should be given as conditions demand, especially to promote rest and sleep. In addition to those previously mentioned, paraldehyde deserves special consideration because it does not depress the heart. It is best administered on shaved ice or in the form of a 25 per cent. solution in aromatic elixir. The dose ranges between 4 and 15 c.c. (drams j–iv).

Digitalis, properly used, is of the utmost value in the treatment of congestive heart failure. It is often the direct means of saving life, especially in the 60 to 70 per cent. of all cases of congestive failure in which there is fibrillation of the auricles. Its usefulness, however, is not limited to this type of case. Digitalis itself is the only member of this group of cardiac stimulants which should be used for oral administration. All the others are absorbed too irregularly or too incompletely to be satisfactory. While different samples of digitalis are absorbed at different rates, the average specimen of good activity is completely absorbed within about six hours after ingestion. Absorption after rectal administration is as complete and as rapid as after oral; consequently the rectal dose is the same as the oral. The lower bowel should be emptied by a simple enema of warm water an hour or two before the digitalis is given. An aqueous extract of digitalis may be used, or the tincture may be diluted so as to reduce the concentration of alcohol to 10 per cent. or less. When a large single dose of the tincture is used some of the alcohol should be evaporated off before dilution to reduce the volume injected. Physiological saline solution and tap water are the best diluents. The total volume of the injection should be about 60 c.c. (2 ounces). The fluid should be warmed to body temperature for administration. The injection should be given slowly through a small catheter, and allowed to run in by gravity.

The total amount of digitalis required on the average to produce full therapeutic action after oral administration is determined on the basis of the body weight of the individual and the biological activity of the drug on the cat. The average total dose of high-grade commercial tincture may be considered 1.5 c.c. for each 10 pounds of body weight, or as 2 minims per pound. The dose of the powdered leaf should be one-tenth that of the tincture. This total is divided for administration into doses of suitable size to produce digitalization at the rate desired. Rapid administration may be accomplished safely, and toxic actions may be avoided, by giving half to three-quarters of the total amount required in the first two or three doses. These early large doses should be given six hours apart to permit complete absorption of each before the next is due. The later small doses may be given three times daily or at four-hour intervals until the desired results are secured. Administration should be stopped or interrupted when the full therapeutic effect has been secured, or on the appearance of the first signs of toxic effects, such as depression, nausea, or disturbances of rhythm.

Congestive failure of moderate severity generally responds satisfactorily to two or three doses of 4 c.c. (dram j) of the tincture, followed by the daily

administration of 4 c.c. divided into three or four equal doses. This should be continued for two or three days. If symptoms are acute it is better to give an initial dose of 8 to 10 c.c. (drams ij–ijss) and one or two subsequent doses of 4 c.c. each, to be followed by the small doses previously mentioned. If splanchnic congestion produces frequent vomiting the initial large dose of digitalis may be administered by rectum. It often suffices to stop the vomiting so that administration may be completed by mouth. In extremely critical conditions an intravenous or intramuscular injection of 0.5 mgm. (gr. $\frac{1}{120}$) of ouabain or 1 mgm. (gr. $\frac{1}{60}$) of amorphous strophanthin may be administered. Oral administration of digitalis should begin immediately after such injection and proceed as usual.

In auricular fibrillation the apex rate of the heart should be reduced to 70 or 80 beats per minute and maintained at that level by the continued use of digitalis. If there are dropped beats due to heart-block, digitalis must be administered slowly and cautiously, if at all, lest the degree of block be increased. If this occurs, the hypodermic injection of 1.0 mgm. (gr. $\frac{1}{60}$) of atropin usually restores conduction. The rate of the heart is rarely influenced to any extent by digitalis when sinus rhythm is present, although benefit often results, particularly in patients with pronounced edema. Cardiac failure with pain may fail to respond to digitalis. Some patients are, however, greatly benefited by the prolonged use of small daily doses (2 c.c.—mxxx) of the tincture.

The administration of digitalis usually produces marked diuresis in edematous patients. If this does not occur, or if it is insufficient to remove the edema and the effusions into the serous cavities, diuretics should be given. The Fothergill, or Guy's Hospital, pill given three times a day is often effective. This contains 65 mgm. (gr. j), each, of calomel, squill, and digitalis. The mouth must be watched carefully as salivation is likely to occur. One gram (gr. xv) of theobromin sodium salicylate, or 0.125 gm. (gr. ij) of theophyllin, may be prescribed three times a day for two or three days. Paracentesis of the chest or abdomen may be necessary to remove pleural transudate or ascites. Occasionally multiple scarification of the legs or the insertion of Southey's tubes may be necessary.

The continued use of such vasodilators as the nitrites is of little or no value in the prevention of heart pain, although these preparations may very effectively cut short an attack. Administration of 2 or 3 gm. of theobromin sodium salicylate daily sometimes prevents the recurrence of pain. The iodids have been used with considerable success in syphilitic conditions and may well be combined with small doses of mercury. The arsphenamins are dangerous in advanced heart failure due to syphilitic myocarditis or aortic and coronary disease: if used at all they should be preceded by administration of iodid and mercury for several weeks. The initial dose of arsphenamin should never exceed 0.4 gm. (gr. vj); increase should be very gradual.

Sudden cardiac dilatation with acute pulmonary edema demands heroic measures. Removal of 500 to 800 c.c. of blood by venesection relieves the heart. One or two hypodermic injections of 1.0 mgm. (gr. $\frac{1}{60}$) of atropin sulphate may be given. A series of injections of adrenalin is often life-saving: five or six doses (0.3 to 0.6 c.c. (mv–x) of the 1 : 1000 solution) should be injected subcutaneously at intervals of ten to fifteen minutes. Half a milligram (gr. $\frac{1}{120}$) of ouabain may be given intravenously. Warmth

should be applied by hot-water bottles and warm blankets. Dry cupping of the chest is sometimes helpful.

When advanced heart failure can not be promptly controlled by the foregoing methods there is extensive damage to the heart which warrants a grave and guarded prognosis. Even under such circumstances, however, prolonged continuation of treatment, including the continued administration of small doses of digitalis (about 2 c.c., ♏xxx, of the tincture daily) may be rewarded by some ultimate recovery of the heart.

After advanced failure has been relieved, the patient needs a long period of convalescence during which the measures for prophylaxis and the treatment of beginning failure should be employed as far as possible.

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SPECIAL PATHOLOGICAL CONDITIONS OF THE HEART

ANEURYSM OF THE HEART

Aneurysm of the Heart (*Mural Aneurysm*).—Aneurysm of the heart may result from sclerosis of the coronary artery with occlusion of the branches by embolism or thrombosis, from syphilitic disease of the coronary artery, from chronic myocarditis, purulent myocarditis, bacterial endocarditis, or traumatic injury. The aneurysm may be single or multiple. It may reach the size of an orange, and be located in any part of the heart, but the most common site is the apex of the heart and the middle or lower third of the anterior wall of the left ventricle, involving also the neighboring ventricular septum; the next most common site is the posterior wall of the left ventricle near the auriculo-ventricular ring. The usual sequence of events is first

sclerosis of the coronary artery with high-grade stenosis or complete occlusion of the coronary artery; then in the area supplied by this artery a myocardial infarct, with necrosis, called "myomalacia cordis" by Ziegler; later the formation of connective tissue scars with a thinning of the cardiac wall, which finally bulges outward as a cardiac aneurysm. On the inner surface, adherent organized thrombi are apt to form which may give rise to emboli. Rarely such an aneurysm may tear or burst, constituting a rupture of the heart. Syphilitic disease of the coronaries is rarer than atherosclerosis.

The clinical picture of those cases secondary to disease of the coronary artery has been best described by M. Sternberg. Patients present (1) one or more attacks of angina pectoris, (2) possibly evidence of pericarditis and myomalacia epistenocardia, (3) a latent period of apparent improvement extending over months or years, (4) the stage of severe cardiac failure, or rupture of the heart.

The diagnosis of aneurysm may be suspected by a history of those various stages, by electrocardiographic evidence of myocardial involvement, by outlining an abnormal area of cardiac dulness beyond the apex beat, and by radiographic findings, but is seldom made with certainty during life. Kraus reported a case with an egg-sized aneurysm of the apex of the heart, secondary to coronary artery closure, which gave a shadow on the *x*-ray plates, but was not diagnosed *intra vitam*. Death from partial cardiac aneurysms usually results from heart failure, and not from rupture.

Aneurysms of the valves of the heart may be either acute or chronic. The acute form is usually of mycotic origin and occurs during the course of a bacterial endocarditis as a small globular sac projecting from an aortic cusp; or it may involve the mitral valve. The chronic aneurysm results from atherosclerotic disease of the valve (Osler)

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RUPTURE OF THE HEART

Rupture of the heart may be either (*a*) spontaneous or (*b*) traumatic in origin. So-called *spontaneous rupture* may result from advanced coronary artery disease, from occlusion of one or more of the coronary arteries, from foci of suppurative myocarditis, from gumma of the myocardium, echinococcus cyst, etc. Disease of the myocardium, such as that seen in obese and alcoholic patients, and pericardial adhesions, are said to predispose to rupture. Quain found that rupture of the heart occurred in areas of fatty degeneration in 77 of his 100 collected cases. The most common site of the tear in the coronary artery cases is the lower half of the anterior wall of the left ventricle, in the area normally supplied by the anterior descending branch of the left coronary artery; next in frequency is the posterior wall of the left ventricle. As a result of closure of the coronary artery and the failure of sufficient collateral circulation, the heart wall becomes the seat of an anemic infarct. The myocardium is weakened over the infarcted area, and as a result the intracardiac pressure may produce an aneurysm at

the point of lowered resistance. The actual site of rupture is sometimes difficult to find, as it may be small and covered by a thrombus or by pericardial adhesions. The blood in the pericardial sac may form a cast of the heart.

Clinically the cases secondary to coronary disease give a history similar to that described under aneurysm of the heart due to arterial disease or occlusion. One helpful sign, if present, is the pericardial friction rub over the infarcted area or pericardial tear (Kernig and M. Sternberg). The rupture which may occur during some physical effort, such as defecation, may be large, and the outcome immediately fatal, or small and gradual, under which circumstances the condition may be prolonged over a period of days. The symptoms of rupture are not characteristic. There may be sharp pain, a sense of oppression, dyspnea, syncope, symptoms of internal hemorrhage, collapse, weak pulse, diminution of heart sounds, signs of pericardial effusion, coma, and death.

The *traumatic ruptures* of the heart are those resulting from contusions, blows, explosions, compression of the chest wall, or penetration of foreign bodies from the esophagus. Rupture of the heart was seen during the Great War without any manifestations on the skin or in the chest wall. The previous condition of the heart muscle and pericardium may play a rôle in rupture. The symptomatology of traumatic rupture is similar to that of spontaneous rupture. Death may not be immediate, but has been delayed as much as two weeks and more from the time of the trauma. In many cases the diagnosis is impossible. The therapy, in so far as it is not surgical, consists of absolute rest, application of an ice-bag to the pericardium. morphin, and possibly the transfusion of blood.

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TUMORS OF THE HEART

Tumors of the heart are rare. They may be divided into primary and secondary new growths. Malignant tumors are rarely primary, but attack the heart by extension from neighboring structures or by metastatic involvement. The primary neoplasms reported have been fibroma, myxoma, myxofibroblastoma, lipoma, lymphangioma, cavernous myoma, and rhabdomyoma. The last mentioned is multiple and has been found associated with sclerosis of the brain and malformation of the kidneys. The other tumors are more commonly found in the auricles (Link). The secondary metastatic growths found have been those originating from renal tumors, melanosarcoma, xanthosarcoma, osteosarcoma, chondroma, thyroid tumors, and carcinoma. New growths may invade the heart by direct extension along the pericardial sac, *e. g.*, sarcoma of the thymus, carcinoma of the lung, pleura, or esophagus. Clinically tumors of the heart give no characteristic symptoms. Evidence of pericarditis, dry, hemorrhagic, or purulent, may be found. In a few cases the tumors have compromised the

bundle of His and given rise to bradycardia and heart-block. A case reported by Krause and another by Ehrenberg gave evidence of their presence by *x*-ray examination. The diagnosis may be suspected if cardiac signs or symptoms develop in the course of malignant disease elsewhere in the body, with signs of pericardial effusion, especially hemopericardium, obstruction of a large vessel, and *x*-ray evidence. The prognosis of malignant cardiac tumors is hopeless.

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PARASITES

The parasites which may occur in the heart are the echinococcus, the cysticercus cellulosæ of tænia solium, and trichina spiralis. They are all rare and their diagnosis almost impossible. The echinococcus (hydatid cyst) occurs most commonly in the right ventricle, and produces no symptoms unless the cyst bursts and thus gives rise to embolic infarcts in the lungs, pneumonia, or pleurisy, or to a blocking of the pulmonary artery. Sudden death has resulted from such rupture. The cysticercus, which is next in frequency to the echinococcus, has been found in the myocardium, but produces no symptoms whatever, or only such general symptoms—dropsy, pectoral pain, and evidence of hypertrophy—as are not sufficiently characteristic to lead to a diagnosis. Trichinæ may invade the myocardium, but their mere presence there does not affect the prognosis. Trichinæ may, through their toxic effect, produce acute myocarditis and cardiac weakness. The prolonged hypotension is vasomotor in origin. The treatment is prophylactic and symptomatic.

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WOUNDS OF THE HEART

Wounds of the heart belong more to the domain of surgery. They may be caused by cutting instruments, resulting in stab wounds, by sharp objects, such as paracentesis needles, by bullets, fractured bones, etc. Exploratory needles penetrating the wall of the heart do not usually cause fatal hemorrhage, but may do so, especially if the wall of the auricle is torn. The whole cardiac wall need not necessarily be penetrated to produce severe symptoms. The chief danger is hemorrhage, not merely from the large loss of blood but from over-distention of the pericardial sac, which compresses the auricles and prevents filling of the heart during diastole.

Other serious complications are hemo-pneumopericardium, purulent pericarditis, empyema, pyo-pneumothorax, adhesive pericarditis and mediastinitis, heart failure, and possibly ventricular fibrillation. The symptoms which lead one to suspect a wound of the heart complicating a wound of the thorax are those of angina pectoris, at times also abdominal pain and spasm of the abdominal muscles; a pulsating stream of blood from the wound, which may be foamy from admixture of air from the lung, and the evidence of severe hemorrhage.

The physical examination may reveal a rapidly enlarging area of cardiac dulness due to hemopericardium, or the presence of the characteristic water-wheel murmurs of pneumo-hemopericardium. With these there is usually all the evidence of severe internal hemorrhage. Stereoscopic x-ray examination or fluoroscopy may locate a foreign body or missile in the heart.

The treatment is largely surgical, consisting of suture of the heart wound. Recovery results in about 35 per cent. of the operated cases. Transfusion of blood is also indicated. Large branches of the coronary artery have been ligated with recovery, as in a case recently reported by Davenport and Smith.

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FOREIGN BODIES

Foreign bodies occasionally penetrate the heart from without through injury, or reach the heart through the bronchi, esophagus, or stomach. Various foreign bodies have been found, such as fragments of projectiles, needles, bullets, broken ends of swords, files, knives, toothpicks, splinters of wood, etc. The embolic route is very rare. Foreign bodies have wandered through the heart and great vessels. They cause little reaction, almost no clinical symptoms, and are usually accidental necropsy findings. Thrombi, more especially the ball-thrombi and pedunculated thrombi, cannot strictly be included among the foreign bodies.

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CONGENITAL HEART DISEASE

Definition.—In the course of intra-uterine life, anomalies in the position and structure of the heart or great vessels sometimes result from faulty development or disease. Such defects, comprising the congenital affections of the heart, usually lead to disturbances in the circulation and give rise to abnormal physical signs.

This group of conditions is of relatively little clinical importance. Many of the infants with such defects die during the first few days or weeks after birth. The etiology is but imperfectly understood. The distinction between congenital and acquired lesions, as a rule, is not difficult. There is no known method for repairing the defect.

Etiology.—Congenital affections of the heart are frequently associated with other forms of imperfect development, notably mental deficiency. They are said to occur more often in first-born children than in later ones. The causes of defective growth are not known. Occasionally it appears that heredity plays a part, in that such anomalies may appear in direct or collateral line for several generations. Instances have been recorded in which infections in the mother during pregnancy, particularly rheumatic fever and syphilis, have been followed by the birth of children with imperfect hearts, although the association between cause and effect has not been definitely established. The rôle of maternal impressions during gestation is now assigned but little importance as a factor in the causation of malformations.

Fetal endocarditis is probably responsible for valvular deformities in a small number of cases. It is almost invariably of the right side, affecting chiefly the pulmonic valves. It is nearly always of the chronic or sclerotic variety and it is often difficult to say whether the lesion has resulted from infection of the heart valves or represents an error in development. In many instances the processes are combined, infection being superimposed upon a structurally imperfect valve. The majority of congenital cardiac lesions can be traced to defective growth.

Morbid Anatomy.—In most cases several lesions are present so that a variety of combinations is possible and is, indeed, encountered. To enumerate them would involve making a catalogue of cardiovascular curiosities and would serve no practical end. For purposes of clinical classification two groups may be distinguished—(1) anomalies of position; (2) anomalies of structure.

(1) Anomalies of Position.—Absence of the heart, *acardia*, and *double heart* are rare monstrosities. In *ectopia cordis* the ventral thoracic wall fails to unite in the midline and the heart may lie outside the chest cavity, though enclosed by pericardium and covered by skin and subcutaneous tissue. The heart may be situated in the cervical, pectoral, or abdominal regions. Under these circumstances, extra-uterine life is rarely possible.

Of some clinical interest are the instances of *dextrocardia*, which may or may not be associated with transposition of the thoracic or abdominal viscera. There is sometimes complete *situs inversus*. Transposition of the large arterial trunks is likewise not uncommon. If unassociated with structural defects, dextrocardia may give rise to neither symptoms, hypertrophy, cyanosis, nor heart murmur and may be accidentally discovered in the course of a physical examination.

(2) Anomalies of Structure.—Structural anomalies may result from incomplete development of certain parts of the heart, such as one of the septa; from fetal endocarditis; or from persistence of fetal conditions, such as the *foramen ovale* or *ductus arteriosus* (Botalli).

In the great majority of cases, several lesions are present, the most frequent combinations being pulmonic stenosis with defective ventricular septum; pulmonic stenosis with defective auricular septum; the three defects associated; or pulmonic stenosis and defective ventricular septum with

patent *ductus arteriosus*. Of 242 cases tabulated by Holt, only 23 showed a single lesion.

Pulmonic Stenosis.—Narrowing of the pulmonic orifice is the commonest form of congenital heart disease. It was formerly regarded as being often the result of fetal endocarditis, but is now usually believed to be due to a failure of proper development of the infundibulum of the right ventricle. The stenosis varies in degree, depending, in a measure, on whether it is located in the muscle of the ventricle, in the infundibular region, or in the valvular ring. Usually, there is an associated defect in the ventricular or auricular septum, or a patent *ductus arteriosus*. The patency of the septum or ductus is to be regarded as a compensatory mechanism for relieving the heightened pressure within the right ventricle.

It is of importance for the practitioner to recognize pulmonic stenosis because of its comparative frequency and its compatibility with life for a number of years. The cyanosis which almost invariably is associated with it requires correct interpretation in order that it may be given proper prognostic significance. Most of the cases of congenital heart disease surviving after the tenth year have this lesion, always accompanied by one of the others of a compensatory character.

Pulmonic Atresia.—Obliteration of the pulmonic orifice is a less frequent but more serious lesion than pulmonic stenosis. The pulmonary artery is very small and there may be persistence of the *ductus arteriosus* together with patency of the *foramen ovale*, or defect in the ventricular septum.

Pulmonic insufficiency is relatively rare. It is usually due to fetal endocarditis.

Tricuspid or *mitral defect* is uncommon. Stenosis or atresia is more frequently seen than insufficiency. *Coarctation of the aorta*, in which condition there is narrowing or complete obliteration of the descending arch at, or immediately below, the isthmus of the aorta, is likewise uncommon. It is sometimes found associated with other defects.

Anomalies of the Cardiac Septa.—(*a*) *Defect in the Interauricular Septum.*—Patent *foramen ovale* is a frequent congenital defect, commonly found in association with pulmonic stenosis or an imperfect ventricular septum. The membrane closing the *foramen ovale* may fail, at one point, to become attached to the ring about it, leaving a valve-like slit. Neither this opening nor small fenestrations which may occur in the membrane are of any clinical significance and are not infrequently encountered in necropsies on persons who have died of various unrelated affections.

(*b*) *Defect in the Interventricular Septum.*—A defect in the interventricular septum is one of the common congenital lesions and in about half the cases is associated with pulmonic stenosis. The opening between the ventricles, under such circumstances, acts as an escape valve for the overloaded right heart. The defect is usually in the upper part of the septum. If the septa of both auricles and ventricles are lacking, the heart consists of only two chambers, as in reptiles. If, in the absence of the ventricular septum, the auricular septum is present, the heart is composed of three cavities—*cor triloculare*. Defect of the membranous septum, when the only lesion present, is not incompatible with a long and fairly active life. Such was the case in the instance of Professor Brooks, of the Johns Hopkins University, who, although he knew from early manhood that he had heart trouble, "accomplished an extraordinary amount of work and lived to be about sixty" (Osler).

Patent Ductus Arteriosus.—An open *ductus Botalli* is rare as a solitary lesion. This fetal vessel, however, frequently remains patent in the presence of pulmonic stenosis, usually in combination with a defect in one or both septa. The blood may thus reach the lungs by an accessory channel when the pulmonic orifice is narrowed. The persistence of the *ductus arteriosus* is often necessitated by other changes in the heart.

Anomalies of the valve cusps are not uncommon and usually involve the semilunar segments at the arterial openings. The segments may be increased or decreased in number. Supernumerary segments, if present, are apt to be small, and are more frequently seen at the pulmonary artery than at the aorta. The bicuspid condition is present more often at the aortic orifice. Recent observations of Thomas Lewis suggest that the bicuspid aortic valve is of more than casual interest and importance. He believes that valves so formed ante-natally are malformations, there being no evidence that they result from fetal endocarditis. Among males reaching adult life and possessing congenitally bicuspid aortic valves, 23 per cent. at least die of active endocarditis. In an unselected series of 31 cases of subacute bacterial endocarditis, 26 per cent. presented bicuspid aortic valves, and among those of the 31 cases in which the aortic valve was the seat of vegetations, 40 per cent. showed the bicuspid malformation. Thus, a congenitally bicuspid aortic valve often appears to determine subsequent bacterial endocarditis owing to a susceptibility to infection induced by the congenital malformation. Why this happens is unknown.

Anomalies of the *auriculoventricular valves* are rarely seen.

Fifteen cases of *congenital heart-block*, with complete or partial auriculoventricular dissociation confirmed by graphic records, have been reported. It is probable that in all of these a congenital malformation of the conduction system was responsible for the cardiac irregularity, although histological study of the heart was made in only one instance.

Symptoms.—The evidences of congenital heart disease are usually apparent soon after birth, but may not manifest themselves until later in life. The onset of symptoms may be definitely related to a contributory cause. In a case observed several years ago, cyanosis first appeared at the age of two on the day following tonsillectomy. Up to that time, there had been no suspicion of a cardiac defect. The child died at the age of six. Occasionally there are no symptoms until after puberty.

Cyanosis is the most striking objective symptom and is responsible for the employment of the term "*morbus cæruleus*" by the earlier writers. The mother often refers to the fact that the child was a "blue baby" at birth. In the severer cases, cyanosis is almost invariably present; but taking into account all varieties of defect, it is observed in about half of the total number. It is conspicuous particularly in the lips, cheeks, nose, ears, finger-tips, and toes. The patient may be of a livid color, as though stained with the juice of blue-berries. In 1861, Knapp called attention to the dilatation, tortuosity, and deep violet color of the vessels in the *fundus of the eye*. If congestion is marked, *retinal hemorrhages* may occur. The factors concerned in the production of cyanosis have not been conclusively established. It is presumably due, in part, according to Lundsgaard and Van Slyke, to the passage of unaërated blood directly from the right heart to the arterial system, in part to deficient oxygenation of the blood in the lungs due to disturbances in the pulmonary circulation. If heart failure is present

and the circulation is slowed, increased oxygen consumption by the tissues, per unit of blood flow, may enter into the group of causes concerned.

Clubbing of the terminal phalanges of the fingers and toes often accompanies cyanosis. The changes affect chiefly the soft tissues, very rarely the bones. The occurrence of *dyspnea* is determined by the character and severity of the lesions. If there is no cyanosis, there may be no shortness of breath. The degree of respiratory discomfort varies, in large measure, with the amount of oxygen unsaturation. In the later stages, when cardiac failure dominates the picture, dyspnea is extreme and is accompanied by other symptoms of myocardial insufficiency. *Hemoptysis* and *epistaxis* are not infrequent.

In the cases showing marked cyanosis *polycythemia* is present. The red blood-cells may vary from 7,000,000 to 12,000,000, and there is a corresponding increase in *hemoglobin*. This has been observed as high as 150 per cent. The leukocytes are increased but little, if at all. The temperature tends to be subnormal. The children rarely thrive; they are undersized and backward in development. Mental retardation may be an associated anomaly or an effect of the circulatory condition. In infants, feeding furnishes a difficult problem. Attacks of *syncope*, *precordial pain*, and *epileptiform convulsions* are sometimes very distressing. In some instances, despite the presence of cyanosis and cardiac enlargement, the patient may make no complaint of discomfort.

Diagnosis.—In the diagnosis of congenital heart disease two distinct problems are presented: first, a congenital must be distinguished from an acquired lesion; second, a precise anatomical differentiation of the various defects may be attempted. The recognition of a congenital lesion is of prognostic importance and is usually relatively easy. The complexity of the numerous combinations of defects and the variability of the physical signs make precise definition of the structural anomalies extremely difficult. In the majority of cases only a probable anatomical diagnosis can be made.

Cyanosis, clubbed fingers, a loud murmur (usually systolic), and cardiac hypertrophy are the chief diagnostic features. Occurring in a young individual who has never had any of the manifestations of rheumatic infection, with a history of symptoms beginning in infancy or early childhood, they are of particular significance. The cases without cyanosis, seen in older children, occasionally offer some difficulty in distinguishing congenital from acquired disease. The intensity of the murmur, the absence of left ventricular hypertrophy, the persistent absence of symptoms, and a lesion which gives no signs of progression favor the opinion that there is a congenital malformation. In anemic children accidental basal systolic murmurs may raise the question of the existence of a congenital lesion. Such murmurs are softer than those due to congenital defects and are unaccompanied by cardiac enlargement or cyanosis. Subsequent examination, when the general condition has improved, serves to decide the issue.

Murmurs are present in practically every case. They are usually systolic in time, and harsh in quality. Though often audible over a wide area, the points of maximum intensity are either at the base or over the body of the heart, very rarely at the apex. A systolic murmur at the base is most frequently due to pulmonic stenosis, less commonly to aortic stenosis. When heard loudest over the body of the heart, especially along the left sternal border, it is sometimes indicative of a defect in the inter-ventricular septum.

In view of the fact that pulmonic stenosis and patency of one of the cardiac septa are so often associated, it is difficult to decide upon which lesion the murmur depends. A *systolic thrill* may or may not be present. It is not of diagnostic importance. *Cardiac enlargement*, especially to the right, is present in most cases.

A patent *ductus arteriosus* is recognized by the presence of a long, loud, continuous murmur with systolic intensification, best heard in the second or third left interspace. As pointed out by François-Franck, this murmur is heard loudly in the left side of the back over the area at which the aorta comes in contact with the chest wall, at the level of the third and fourth dorsal spines. The associated lesion is almost always pulmonic stenosis.

Abnormal positions of the heart cause the *apex beat* to appear in an unusual location and the *cardiac outline*, as mapped out by percussion, does not occupy its customary place. Confirmatory evidence is afforded by *x*-ray examination. It is difficult to recognize abnormalities in the origin or position of the great vessels. Under the fluoroscope, a patent *ductus arteriosus* may sometimes be seen as a pulsating shadow in the region usually occupied by the pulmonary artery and left auricle. In pulmonic stenosis the pulmonary artery is often dilated.

Electrocardiographic examination is of particular diagnostic aid in dextrocardia. In this condition, the cardiac axis is rotated, so that with Lead I the usual waves are seen as in a mirror image. Lead II corresponds to the usual Lead III, and Lead III to the usual Lead II. In other forms of congenital defect, various types of change have been recorded. The excursions are often wide and there may be right or left ventricular preponderance. In congenital heart-block, electrocardiographic records clearly demonstrate the disturbed cardiac mechanism.

Prognosis.—In general, the prognosis is grave. It varies, as a rule, directly according to the severity of the symptoms, especially the degree of cyanosis. Of 225 cases collected by Holt, 60 per cent. died before the end of the fifth year, and nearly half of these during the first two months; 16 per cent. lived over sixteen years and 8 per cent. over thirty years. The lesions compatible with the longest life are minor septum defects or pulmonic stenosis which is accompanied by compensatory anomalies, such as patent *ductus arteriosus*. The intensity of the murmur is of no prognostic import. Patients with serious congenital heart disease are particularly susceptible to respiratory infections. A number die of bacterial endocarditis or pulmonary tuberculosis. Any acute malady may be fatal.

Treatment.—There is no method now known for remedying structural defects of the heart. It is conceivable that a surgical technic for such a purpose may be developed. The children should be cared for so that infections, particularly of the respiratory tract, are avoided in so far as possible. The amount of physical activity which is permitted must be determined by the exigencies of the individual case. Heart failure, if present, is managed in the usual manner. Symptomatic treatment is given as required.

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ANGINA PECTORIS

(*Stenocardia, Breast pang*)

Definition.—Angina pectoris is not a disease in the true sense of the word, but a clinical syndrome characterized by paroxysmal attacks of pectoral or precordial pain, syncope, and a sensation of intense anxiety. The pathology is highly diversified.

Incidence.—That the incidence is increasing is unquestionably demonstrated even by statistics which take into consideration the fact that more accurate diagnosis obviously increases the number of cases. In rural districts angina is less common than in cities, probably because physical labor is less conducive to its development than is the strain of business or professional life. Its infrequent occurrence among the patients in general hospitals and its high incidence in private practice may doubtless also be explained in the same way, although its occasional sudden onset and abrupt termination might prevent entrance to the hospital.

Angina pectoris is an affection of the *intellectual*, not of the *laboring classes*. It occurs with great frequency among educated people of all races. Physicians seem to be particularly susceptible; but lawyers, brokers, financiers, actors, artists, and writers are also frequently subject to it. Indolence and leisure, overeating, smoking, and drinking do not appear to be predisposing factors.

The influence of *sex* upon the incidence is well shown by Osler's statistics. In his series of observations there were 256 men as compared with 44 women. Although so-called domestic women seem particularly insusceptible, the occurrence of angina pectoris in women is increasing in metropolitan districts. In the writer's series of 1500 consecutive cases in New York City, 47 were in women.

Age is a determining factor. The syndrome is rarely observed in patients below fifty; and Osler's aphorism, that when the subject is less than forty years of age, anginal pain must be considered syphilitic in origin unless definitely proved otherwise, is probably well founded.

That a predisposition may be *inherited* seems to be demonstrated by the frequent occurrence of angina in many old families of New England ancestry, and by the fact that familial arterial disease is almost always associated with the syndrome.

Etiology.—The cause of angina pectoris has not yet been satisfactorily explained. Mackenzie emphasizes the great variation in the susceptibility of different individuals to pain, and states that cardiac pain depends upon three factors: malnutrition, which may result from arterial spasm or occlusion; muscular cramp caused by overstimulation; and such muscular exhaustion as might follow degeneration of the cardiac muscle. That either of these factors is always associated with its occurrence cannot be unconditionally assumed. Evidence of arhythmia was found in 1.4 per cent. of the writer's cases. Indeed, electrocardiographic records made even during the height of an attack are frequently perfectly normal. Verdon attributes the pain to "necrosis" of segments of the spinal cord; and Bamberger and von Neusser assert that it is a reflex response of the vagus to some unusual stimulus. Alexander Lambert has elaborated this theory in his recent discussion of this condition. Since the very diversity of these theories is proof

of insufficient knowledge, it is wiser for the practitioner to consider the syndrome the result of definite cardiac lesions.

Syphilis is undoubtedly the most frequent cause of anginoid pain in patients less than forty years of age. It may also be of etiological importance when the typical syndrome develops later in life. It was the apparent cause in 4 per cent. of the author's cases. It may affect the aorta or directly establish coronary arteritis, or lead to narrowing of the aortic orifices of the coronaries with ensuing myocardial inflammation or degeneration. Aortitis, specific or otherwise, is one of the lesions most frequently associated with angina pectoris.

The frequency with which angina pectoris, often of a transitory type, develops after acute infections is evidence of the causative rôle of myocardial degeneration and inflammation. In a series of 200 consecutive cases of myocardial disease the writer found angina a prominent symptom in 29 patients. The disturbances following influenza are a good example of this.

Morbid Anatomy.—Cardiac lesions are present in the majority of cases, and may be of many types. Often there seems to be no relationship between the severity and form of the lesion and the character of the syndrome which it produces. Abnormalities of the coronary blood-vessels, which are the lesions most commonly associated with angina, do to some extent, however, determine the type of the clinical manifestations. Acute obstructive lesions of these vessels cause sudden violent crises which are liable to be immediately fatal or to be followed by less severe and briefer attacks. Aortitis, which is at times obstructive, frequently involves the mouths of the coronary vessels. This type of lesion is often associated with syphilis or physical strain. Although coronary sclerosis is so commonly associated with angina pectoris in man that there can be no doubt of its relationship to the syndrome, it is very difficult to understand why it can so often become extensive without causing evidences of the disease. That it is not the only lesion responsible for the symptoms is shown, however, by the fact that myocardial degeneration or myocarditis are at times the only anatomical abnormalities to be found at autopsy; indeed, Osler, Lambert, and others cite the occurrence of angina pectoris without any demonstrable macroscopic lesions. Any type of coronary disease may be associated with this disturbance; acute thrombosis, for instance, or embolism, or a chronic calcareous degeneration.

Several theories have been advanced to explain the occurrence of heart pain. The most modern conception is that the pain is due to abnormalities in the contraction of the heart muscle. It is, therefore, analogous to pain arising from disordered muscular contraction of other hollow viscera. The abnormality in the muscular function of the heart may result from disease of the myocardium; from a deficiency of the blood-supply caused by aortic or coronary disease; from muscular exhaustion or intoxication; or from combinations of these factors. In the last analysis, the pain of angina pectoris is probably always an expression of myocardial exhaustion.

Symptoms.—The symptoms of angina pectoris are quite characteristic. During an attack the *pain*, which is almost constant, is located primarily in the precordial region. From there it is reflected extensively; most often down the left arm and forearm to the finger-tips, but at times to the right upper arm, the back of the neck, and down to the thigh. Not infrequently it is reflected into the abdomen, perhaps to the epigastrium, the region of

the gall-bladder, or the appendix. Probably wherever organic lesions of a painful character are located, reflected pain of cardiac origin is likely to be referred. The pain, while usually paroxysmal in character and ordinarily not long-continued, may persist for hours or even remain almost constant for days—especially when thrombosis or embolism has taken place. Hence pain apparently located in other viscera may really originate in the heart. Closely associated with the pain, but not dependent upon it, is a sense of *anxiety* or of *impending death*, which is always severe and occasionally entirely out of proportion to the severity of the pain. This is the most characteristic feature of angina pectoris.

The *appearance of the patient* during the attack is characteristic. A position of fixation, either standing, seated, or in bed, is assumed. No unnecessary movements are made and, notwithstanding the agony, the patient is mute, or occasionally perhaps gives a suppressed groan. The face is ashen and covered with cold sweat; the lines deepen; the eyes protrude.

As a rule the *pulse* is slow, soft, and manifests no irregularity not present during normal periods. The *blood-pressure* is ordinarily that usual for the individual. It may be very low. Hypertension, unless primarily concerned, is the exception during attacks. The *heart sounds* are usually distant and weak. *Dyspnea* is notably absent or slight. The breathing is slow and measured. Occasionally, particularly in instances of coronary embolism, fine crackling râles may be heard posteriorly at the bases. Acute pulmonary edema may characterize some cases.

At the conclusion of a paroxysm the patient assumes an attitude of relaxation or relief; large quantities of clear urine may be passed; and profound sleep is likely to ensue. The signs of exhaustion are proportionate to the duration and severity of the attack.

There are no characteristic physical signs other than the facies of the patient during the paroxysm. Physical indications of the primary condition or of associated lesions concerned may, of course, be evident, but they bear no characteristic relation to the attack.

Diagnosis is difficult. The condition must be differentiated from very numerous painful conditions—especially those of a paroxysmal character which occur in the chest or abdomen—from gall-stone or renal colic; neuritis, myalgia, the pain of cardiac dilatation and of pericarditis; and from a vast assortment of neuroses with or without actual organic cardiac disease. The manner of onset is of considerable diagnostic significance. An attack of true angina is precipitated ordinarily by some physical or emotional stress, however slight. The frequent onset of the disturbance during sound sleep is presumably explained by anemia of the cardiac muscle. A history of previous similar attacks can usually be obtained. In most cases the paroxysm is preceded by a sense of fulness or pain behind the *manubrium sterni*. The almost universal *characteristic anxiety* is a diagnostic feature of great value. It should be noted that true anginal pain is transmitted chiefly to the areas of peripheral distribution of the upper four thoracic nerves, the eighth, third and second cervical, and the fifth cranial, and that the application of counterirritants to these areas often relieves rather than intensifies this symptom. The general attitude of the patient, previously emphasized, is probably one of the most characteristic features of the disease. While most patients with hysterical or neurotic disturbances are voluble, throw themselves about the bed, and insist on attention from the bystanders, an

individual with true angina remains perfectly silent and still. While there are as yet no absolutely pathognomonic electrocardiographic indications of angina pectoris, the electrocardiograph is of increasing value in the diagnosis of the syndrome when coronary lesions or aberrations of conduction are shown. Negative electrocardiographic findings are of neither negative nor positive value. Positive findings are very valuable when present. Many authors consider as true angina the painful symptoms occasionally produced by excessive use of tobacco, tea, or coffee, but the writer does not believe this wise because of the absolutely different prognosis. He has never known tobacco, coffee, or tea angina to prove fatal. A well-known authority on angina pectoris, himself an excessive user of tobacco, finally became so prostrated by the frequency and severity of the paroxysms that he was obliged to go to bed. Within one month after ceasing the use of tobacco he was able to go on a hunting trip, carrying a heavy pack on his back, and paddling for long distances. Such recovery is never observed in true angina pectoris.

Prognosis.—The outlook is always serious, but not nearly so much so in many instances as it was thought to be in the past. Many patients with transitory or curable lesions recover entirely. There is not, unfortunately, any absolutely certain means of distinguishing clinically between the most serious types and those with a favorable prognosis. Some patients die during the initial attack, while others live for years—the difference depending in part on their manner of life, but, of course, primarily on the nature of the causative factors. Recovery is undoubtedly complete in a good many cases. Death often occurs during apparently mild attacks, thought to be due to remediable lesions. Angina pectoris must always, therefore, be considered serious until careful study of the ability of the patient to adapt himself to the new mode of life, and the conditions and habits most suitable for the individual, can determine the outlook more accurately. Each case is a problem in itself. The manner of death, which is extremely variable, is, for the most part, determined by the type of lesion. Coronary embolism is probably most frequent.

Treatment.—The treatment of angina pectoris is primarily designed to relieve the immediate attack, and to cure or ameliorate the causative condition. Undoubtedly the *drug* which is used most successfully to relieve the paroxysms is morphin, given hypodermically or intravenously. The dose should be sufficiently large, if possible, to check the pain promptly, because with the cessation or control of pain the immediate danger to life is either greatly reduced or eliminated. When coronary embolism has taken place, or when for any other reason an attack is protracted, it has proved wise to keep the patient continually under the effects of morphin until pain has entirely ceased. In one instance, increasing massive doses of morphin were administered for three weeks before the pain finally stopped. Two years later the patient was still able to get about and to enjoy life temperately. Next to morphin, the nitrites are most successful in the treatment of the paroxysm. The form to be employed depends greatly on the reaction of the individual. Liquid preparations of nitroglycerin are the most effective of all those taken orally. When a physician or nurse is at hand the nitroglycerin may be administered hypodermically, and certain patients may be advisedly provided with sterile hypodermic units. New patients should perhaps be first treated with small doses, but if only larger

doses prove effective, they should be given promptly. Nitroglycerin in tablet form may be taken by mouth or dissolved on the tongue. As inert preparations are very likely to be sold, only tested tablets, preferably of the hypodermic type, should be employed. Many patients obtain full and immediate relief from the inhalation of the fumes of amyl nitrite (ampoules or pearls) which, if it is effective, is probably the most convenient form of nitrite. Whenever possible, the patient should sit, lie down, or support himself against some stable object when taking any of these drugs. The dose should be repeated until relief is complete and the patient should not be moved until it is certain that the paroxysm is over. Patients to whom nitrites are given should be warned of their action in order to prevent fear of the throbbing of the head and flushing of the face. Chloroform, though very dangerous in some cases, may occasionally be used advisedly.

Application of heat over the heart or painful areas not infrequently gives great subjective relief.

Preventive or *curative* treatment is of course determined for the most part by the etiology of the particular case under observation. Every possible effort should be made to determine the fundamental cause of the disturbance. The angina of relatively early syphilis, and even in some instances of late syphilis, may be entirely and permanently cured. That due to myocardial disease may often be greatly benefited by the administration of adequate doses of *digitalis*, but in other types this drug may aggravate or produce the attacks. In many syphilitic cases, and in others of different origin, the *iodids* may be beneficial, and, even if the Wassermann test is negative, administration of *mercury* may occasionally prove very useful if followed by a consistent course of antisyphilitic treatment. Angina at times improves greatly after a prolonged period of *rest in bed*, but not always. Some patients require much quiet, but others are certainly more content and less liable to attacks if they are permitted certain reasonable activities and occupations. As there is always great danger in over-distention of the gastro-intestinal tract, mild, rarely active, catharsis is desirable. It is almost always necessary to avoid *physical effort* and also *emotional stresses*, fits of anger, sexual relations, emotional shocks, and the like. Some patients appear to improve after the moderate use of alcohol, but excessive amounts should never be taken. *Tobacco* is tolerated very well by some individuals, in fact, it may lessen the occurrence of attacks, but as a rule it is definitely harmful and should not be used. *Cold baths*, or sudden exposure to the cold air, frequently precipitate attacks. If the angina is of gouty origin, administration of colchicin or atophan and a suitable diet may apparently cure the disease. Night attacks may sometimes be prevented by the routine use of a *sedative*. Occasionally tea, coffee, and other *stimulants* lessen the frequency of the attacks.

Of late much interest has been directed to the relief or cure of angina pectoris by surgical means. Favorable results have been widely reported (Lillienthal, Werikebuch, Coffy and Broun, Jennings, and others). The following operations have been variously performed: resection of the stellate ganglion on one or both sides (advised by Jonnesco); section of the depressor nerve on the left side, occasionally bilaterally; section of the sympathetic cord above the stellate ganglion; cervical sympathectomy without resection of the stellate ganglion; division of a nerve-fiber emerging from the vagus on the left or on both sides; section of the cervical sympathetic to-

gether with the superior cardiac nerve on the left side; section of the cervical sympathetic above the inferior cervical ganglion, including section of the vertebral nerve on the left side; and modifications or various combinations of these operations. Recently Swetlow and Schwartz have treated the condition with varied success by paravertebral alcohol block. Except when no anatomical disease of the heart, coronary, or aorta can be recognized, all of these methods are probably inadvisable other than as a desperate attempt to relieve intolerable suffering. Mackenzie has aptly pointed out that when there is actual anatomical disease, operative methods only serve to relieve the symptom, and that the full danger of the syndrome persists or is accentuated by removal of the protective symptom of pain.

HARLOW BROOKS.

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DISEASES OF THE ARTERIES

SYPHILITIC AORTITIS AND ANEURYSM

History.—While the relationship between aneurysm and syphilis was suspected as early as the 16th century, by Paré, and later by Lancisi (1728) and Morgagni (1761), it was not until 1876 that Francis H. Welch first described accurately the gross and histological changes which take place in syphilitic aortitis.

Years later (1888), Döhle published a comprehensive report on syphilitic aortitis, and for a time the disease was called Döhle-Hellerschen aortitis. Döhle defined mesaortitis as a specific inflammation of the adventitia and media which terminates in cicatricial deformity.

Schaudinn and Hoffmann, in 1905, were the first to direct attention to the *Treponema pallidum* as the specific cause of syphilis. In 1905–1906, Wassermann described the complement-fixation test which bears his name. In 1906, Reuter demonstrated the *Treponema pallidum* in sections of syphilitic aortas. Rebaudi, and Roch and Wiesner found spirochetes in the aortas of patients with congenital syphilis. Vanzetti reproduced lesions similar to those found in humans by injecting material obtained from the testicles of syphilitic rabbits into the sheaths of the carotid arteries of other rabbits.

This chain of evidence, amply corroborated, established the fact that syphilitic aortitis is a specific inflammation of the aorta produced by the *Spirocharta pallidum*.

Etiology.—The specific cause of all syphilitic lesions is the *Treponema pallidum*. This organism has a predilection for the vascular system and

is especially prone to invade the arteries of the brain and the aorta. Spirochetes have been demonstrated in the lesions produced in the aorta. In the late primary and early secondary stages of syphilis, the spirochetes are in the general circulation, and invasion of the aorta probably takes place at this time.

That syphilitic disease of the cardiovascular system is of frequent occurrence is demonstrated by the fact that from 4 to 7 per cent. of all patients who come to autopsy in general hospitals show syphilitic aortitis, and that from 15 to 25 per cent. of all organic heart disease is caused directly by syphilis. It has been said that syphilitic aortitis accompanies 70 per cent. of all visceral syphilis.

Syphilitic disease of the aorta is about three times as common in males as in females. The negro race is peculiarly susceptible. Three-quarters of all the cases occur in individuals between the ages of thirty and fifty-five; that is, the age incidence of syphilitic aortitis lies midway between those of rheumatism and atheroma.

Morbid Anatomy.—Syphilis shows a distinct disposition to attack the aorta. The inflammatory process generally originates just above the root of the aorta, whence it extends upward through the ascending and transverse arches, as well as downward toward the aortic ring. Aortic insufficiency may be caused by changes in the ring itself, or by thickening and wrinkling of the aortic valves. Weakening of any portion of the wall may produce diffuse dilatation or sacculated aneurysm.

More or less narrowing of the mouths of the branches arising from the arch of the aorta is produced by their involvement in the process. The mouths of the coronary arteries are also frequently involved, but the disease rarely extends any considerable distance into the arteries themselves.

On gross section, over the inner surface of the aorta, in the earlier stages of the disease, there may be seen pale gray, succulent, isolated, wheal-like patches, varying in size from 0.5 cm. to 2.5 cm. in diameter; or similar patches which may be confluent and involve the entire circumference of the aorta. In the later stages, the patches are tougher, more extensive, and intermingled with pitted, scarred, puckered areas. The walls are markedly indurated in some spots and thinned in others. The almost complete absence of fatty degeneration and calcification in the lesions is in contrast to the changes which take place in atheroma of the aorta.

Infection of the aorta takes place either by way of the *vasa vasorum* or through the lymphatics. The earliest lesions show infiltration about the *vasa vasorum* by lymphocytes and plasma cells. The most striking changes, however, are noted in the media, where there are many newly-formed vessels and infiltration with small round cells and plasma cells, with here and there slight breaks in the elastica. In the early stages of the disease, there are very slight or no changes in the intima. As the disease advances, or in severe infections, the lesions are much more extensive in the adventitia and media; cellular infiltration in the adventitia is more pronounced; and in the media areas of coagulation necrosis surrounded or even infiltrated by round cells and plasma cells are found. There is also marked fragmentation or complete destruction of the elastica. In still more advanced stages of the disease, all three coats of the aorta may be involved in an inflammatory, necrotic process, although the lesions of the intima are usually confined to a compensatory thickening due to cellular proliferation.

The attempt to repair the damage wrought by granulomatous inflammation leads to a replacement fibrosis, and the connective tissue formed in this process later undergoes cicatricial contraction. It is this change which is responsible for the scarring, wrinkling, and pitting of the aorta which may be noted on gross examination.

Symptoms.—A *latent period* of some fifteen or twenty years may intervene between the appearance of the primary sore and the development of symptoms referable to the aorta. In rare instances, however, the disease may progress so rapidly that death may result from a ruptured aneurysm within a year after infection.

A gradual, symptomless *onset* is the rule. The appearance of premature systoles and tachycardia during the secondary stage of syphilis suggests early involvement of the cardiovascular apparatus.

The *later manifestations* of the disease are due to dilatation of the aorta —the involvement of the mouths of the coronary arteries interfering with the intrinsic blood-supply to the heart—secondary affection of the aortic ring and the aortic valves; changes in the myocardium; and finally, to an inflammatory reaction in the tissues about the root of the aorta. The most common subjective manifestations of syphilitic aortitis are substernal oppression, pain, and dyspnea. They may occur with or without objective signs of dilatation of the aorta or involvement of the aortic valves.

Substernal oppression varies from a moderate sense of discomfort to severe, agonizing pain. It is usually referred to the upper portion of the sternum, and is variously described as a sense of weight or a feeling of constriction, as if the chest were being squeezed in a vise. The pain is knife-like or burning in character, and may radiate to the left arm or to both arms, into the neck, or even into the back or epigastrium. Attacks of pain or substernal oppression may occur only during exercise or under emotional stress, but they may also take place at rest in the recumbent position. Once such attacks begin, there is a tendency for them to increase in frequency and severity.

Dyspnea in syphilitic disease of the aorta may occur only during exertion; may be associated with evidences of cardiac decompensation; or may be paroxysmal. The last type of dyspnea is almost pathognomonic of the disease. Paroxysmal dyspnea is abrupt in onset and agonizing in character. Without any premonition of an attack, the patient is suddenly seized with shortness of breath; the respirations increase in number; and expiration is difficult. The accessory muscles of respiration are brought into play. At the onset, the patient may cry out in fear or agony. If one listens to the chest during the seizure, sibilant breathing can be heard such as obtains in asthma from any cause. During the attack, the pulse rate is increased and the blood-pressure is raised. There is often deep cyanosis and profuse sweating. Pain may or may not be associated with dyspnea. Fortunately a seizure of paroxysmal dyspnea is of short duration, rarely lasting more than fifteen minutes, and frequently not over five. Such attacks may be repeated several times daily, or only occasionally during the entire course of the disease. Death may occur during a seizure. It has been suggested that paroxysmal dyspnea is the result of disturbing reflexes set up by inflammation at the root of the aorta, where the nerve supply is rich.

Physical Signs.—The physical signs of syphilitic aortitis are those

associated with dilatation of the aorta, aneurysm, aortic insufficiency, and myocardial insufficiency.

Dilatation and aneurysm will be discussed as a complication of aortitis. For the physical signs of *aortic incompetency* and *myocardial inefficiency*, the reader is referred to the appropriate chapters.

Fever of unexplained origin may occur during the course of syphilitic aortitis, and disappear when antiluetic treatment is instituted.

Hypertension and cardiac hypertrophy are not a part of the picture of uncomplicated aortitis of luetic origin.

There is frequently a moderate degree of *secondary anemia;* in some instances, the lymphocyte count is increased. The Wassermann reaction is positive in rather more than 90 per cent. of the cases.

Diagnosis.—Syphilitic aortitis may be latent. There are no subjective symptoms and nothing is revealed by various methods of examination. A history of syphilis, stigmata of the disease in other tissues, and a positive Wassermann should always be considered potential evidence of syphilitic involvement of the aorta.

In another type of case there may be very definite subjective symptoms but no objective findings which can be demonstrated by physical examination or by *x*-ray. Paroxysmal dyspnea is extremely suggestive of syphilitic aortitis. Anginal attacks occurring in an individual less than fifty years of age should always arouse suspicion of syphilitic infection.

The age incidence of syphilitic disease of the aorta is somewhat helpful in differentiating it from *atheroma of the aorta*, which is prone to occur in the declining years of life, and from *rheumatic aortitis*, which occurs in adolescence or early adult life. Syphilitic aortitis almost invariably occurs at a time of life a bit late for rheumatism, and a bit early for atheroma.

Aortic insufficiency uncomplicated by *mitral disease* is usually syphilitic.

There is still a third group of cases, in which the subjective symptoms can be readily and satisfactorily checked by physical examination, fluoroscopy, and *x*-ray. The diagnosis in this type will be discussed with aneurysm of the aorta.

Prognosis.—The prognosis in a given case varies directly with the stage in which the disease is recognized. If treatment is not begun until definite symptoms are present, or until physical signs of syphilitic changes in the aorta appear, the prognosis is bad, in spite of any therapeutic measures which may be instituted.

Over two-thirds of the patients die within a year of the advent of signs and symptoms if untreated. The expectancy of life may be somewhat more than doubled by treatment.

Death may be caused by some intercurrent infection; by cardiac decompensation resulting from the extension of the disease to the aortic valves; by myocardial disease; or may take place during an attack of paroxysmal dyspnea, angina pectoris, or after rupture of an aneurysm.

ANEURYSM

Sir William Osler defined an aneurysm as "a tumor containing blood, in direct communication with the cavity of the heart, the surface of a valve, or the lumen of an artery."

The walls of a *true aneurysm* are composed of at least one of the coats

of the artery, while in a *false aneurysm* the coats of the artery have been ruptured, and the walls of the sac are composed wholly or in part of surrounding tissues or newly-formed connective tissue.

History.—Claudius Galen, who died about 200 A. D., recognized two forms of aneurysm, one caused by dilatation, the other by a wound of the arterial wall. Vesalius, in the middle of the 16th century, was the first to recognize clinically aneurysms of the thoracic and abdominal aortas. Lancisi, in 1728, and later Morgagni, in 1761, recognized syphilis as a probable cause of aneurysm. It was not until early in the 20th century, however, that the relationship between syphilis and aneurysm was firmly established by the discovery of the *Treponema pallidum*, and its demonstration in sections made on syphilitic aortas.

Types of Aortic Aneurysm.—I. *Diffuse dilatation*, which is either limited to a segment of the aorta (fusiform dilatation), or extends for a considerable distance along the aorta (cirsoid dilatation).

II. *Sacculated aneurysm*, the most common type, which consists of a circumscribed bulging of the aorta in direct communication with the lumen of the vessel, and is caused by weakening of the arterial wall by disease.

III. *Dissecting aneurysm*, which is due to rupture of the intimal coat of the aorta, which permits the blood to force its way between the intima and media.

IV. *Arteriovenous aneurysm*, in which there is a communication between the aneurysm and a large vein, such as the superior vena cava. If the communication is direct, it is called an *aneurysmal varix;* if the sac is interposed between the aorta and the vein, it is known as a *varicose aneurysm.*

Morbid Anatomy and Etiology.—There are always two factors involved in the formation of aneurysm: degeneration or destruction of the mesial coat, with consequent weakening of the vessel wall; and strain. By far the commonest cause of mesaortitis, though not the only one, is syphilis. If the media is destroyed throughout the circumference of the vessel, fusiform dilatation occurs under the strain of ordinary blood-pressures. If there is an area of focal necrosis in the media, the intima underneath it gives way, and a sacculated aneurysm results. As the aneurysm gradually increases in size, the movement of blood within the sac is slowed, and clotting takes place.

An attempt at healing in an aneurysm is made by the formation of new connective tissue in the adventitia and in the adjacent structures, and by the production of fibrin within the sac. Healing with complete cure is possible, but it is not common because the aneurysmal sac, under the constant strain of the blood-pressure, usually increases in size more rapidly than sufficient connective tissue and fibrin can be formed.

The lining of large aneurysms of the aorta is composed of the adventitia; or, in advanced stages of the process, when the adventitia itself may be destroyed, of adjacent tissues, such as bone, skin, connective tissue, etc.

In the cross section of an aneurysmal sac, the tough capsule can be seen and within more or less organized fibrin which is laid down in laminæ or layers.

The constant expansile pulsation of a large aneurysm has a very definite effect on adjacent structures, causing erosion of bone, for instance, and compression of the esophagus, trachea, bronchi, lungs, nerves, and veins. Long-continued pressure on a bronchus may produce definite changes in the lung, with the formation of bronchiectatic cavities and abscesses of the lung.

These, because of their similarity to tuberculosis, have been termed *aneurysmal phthisis.*

Location.—Something over 75 per cent. of the aneurysms of the aorta are situated in the ascending, transverse, or descending arch. Involvement of the thoracic and abdominal aorta is relatively infrequent.

Symptoms.—Under certain conditions an aneurysm may produce no symptoms; under others, the symptoms are mainly those of the syphilitic aortitis, which forms the basis upon which the aneurysm develops. In most cases, however, the symptoms of aneurysm are due to the effects of erosion and pressure on neighboring structures and tissues, and, in consequence vary according to the part of the aorta which is involved. As a general rule, aneurysms of the ascending aorta are more apt to produce physical signs, while those of the transverse portion of the arch cause more or less definite symptoms of pressure and few physical signs.

Pain is the most common subjective manifestation of aneurysm. It may be constant and boring in character, because of erosion of bone; may be intermittent and neuralgic, on account of irritation of nerve fibers; or may amount to nothing more than the substernal oppression or discomfort which is associated with syphilitic aortitis. It is less apt to be severe when the aneurysm involves the ascending arch. A small aneurysm of the transverse arch may cause intense pain, without demonstrable signs. Growth of the aneurysm backward may cause agonizing pain, when there is pressure on the spine. Aneurysms of the descending arch and thoracic aorta are most apt to produce severe pain by pressing on the intercostal nerves and causing erosion of the spine. Constant, dull, boring pain may be the first manifestation of aneurysm of the abdominal aorta.

Dyspnea.—Apart from the dyspnea on exertion and the paroxysmal type associated with syphilitic aortitis, dyspnea may be due to constriction of the trachea, a main bronchus, or the lung itself, by the aneurysmal sac. Aneurysms of the transverse arch are more likely to cause pressure on the trachea while aneurysms of the descending aorta are apt to press on the lung or a main bronchus.

Cough may be an early symptom, due to pressure on the trachea, the bronchi, or the lungs. It is frequently paroxysmal in character and brassy in quality.

Hoarseness occurs most frequently with aneurysms of the transverse arch, because of pressure on the left recurrent laryngeal nerve. The later manifestation of such pressure is adductor paralysis of the vocal cord, with changes in the voice, which vary from weakness and hoarseness to complete aphonia.

Dysphagia is most commonly observed in aneurysm of the transverse or descending aorta. It may be due to direct pressure on the esophagus, with or without ulceration, which causes difficult or painful swallowing; or to irritation of the left recurrent laryngeal nerve, which sends branches to the esophagus.

Aneurysm of the *abdominal aorta* is relatively infrequent; not more than 10 per cent. of aortic aneurysms occur in this portion of the vessel. The symptoms are often obscure—pain of a severe, boring, constant character, due to pressure on the spine, being the most common subjective manifestation. Among the other symptoms of pressure are dysphagia, due to pressure on the lower end of the esophagus; intestinal obstruction; oliguria, due

to pressure on the renal veins; hydronephrosis, secondary to pressure on the ureter; and edema of the lower extremities, caused by pressure on the inferior vena cava.

Physical Signs.—The signs of aneurysm of the aorta are more definite and consequently more important than the symptoms. In order that a proper physical examination may be made in a case of suspected aneurysm, the patient should be stripped to the waist, and examined in a good light, for the most important signs of the disease are revealed by inspection, palpation, and percussion.

Inspection.—Pressure on the large venous trunks situated within the thorax may cause *edema* of the areas which drain into these veins; or dilatation of the veins of the upper portion of one or both sides of the chest, neck, and arms may be associated with more or less cyanosis.

Inequality of the pupils may result from pressure on the sympathetics—stimulation or irritation causing dilatation, and paralysis or destruction, contraction.

Pressure on the left recurrent laryngeal nerve produces first *paralysis of the abductor fibers*, with fixation of the vocal cord in the midline, and later *adductor paralysis*, with recession of the cord in complete paralysis.

Pulsation, systolic in time, sharply circumscribed or diffuse, may be observed in the second and third interspaces to the left or right of the sternum, over the manubrium, in the episternal notch, or posteriorly in the left interscapular region or below the angle of the left scapula, depending upon the size and location of the aneurysm.

Palpation.—On palpating the area overlying an aneurysm, distinct *hearing pulsation* may be noted. If the chest has been eroded, this pulsation often has a definite expansile quality. *A shock*, diastolic in time, is a common sign elicited by this method of examination. A *systolic thrill* is felt in many instances, if the sac is not filled with a clot. There may be *tenderness* on pressure over the sternum. *Tracheal tug* is present in aneurysms of the transverse arch of the aorta, when the sac has become adherent to the trachea. It may be satisfactorily demonstrated if, standing behind the patient, the examiner places the first two fingers of each hand beneath the cricoid cartilage and exercises slight traction, while the subject extends the neck and hold his breath. If an aneurysm is so situated as to involve the mouth of the innominate artery, or if it lies between the innominate and the left subclavian, there may be a distinct *difference in the radial pulses* on the two sides. If the aneurysm blocks or compresses the innominate artery, the radial pulse on the right side will often be found to be distinctly weaker than that on the left, while, if the aneurysm occupies a position between the innominate artery and the left subclavian, the left radial pulse will be found to be delayed and weak, in comparison to that on the right. Similarly, there may be distinct *differences in blood-pressure* on the two sides.

Percussion.—*Dulness* on percussion is perhaps the most valuable single sign of aneurysm. The normal dulness over the manubrium is converted into flatness, and diminished resonance is frequently elicited by percussion in the first and second interspaces, to the right or left of the sternum. Posteriorly, there is, in the normal chest, dulness over the first three dorsal vertebræ, while the percussion note over the remainder of the thoracic vertebræ is resonant. If aneurysm is present, one may find dulness on percussion which extends below the third dorsal vertebra. If

the aneurysm involves the descending aorta, this may be demonstrable in the left interscapular region or at the angle of the left scapula.

Auscultation.—The signs elicited by auscultation are less important, from a diagnostic standpoint, than those just described. The most constant and the most characteristic auscultatory sign is a loud, ringing *aortic second sound*. A harsh, high-pitched *murmur*, systolic in time, is frequently heard over the area occupied by the aneurysm. A diastolic murmur may be present. The *heart* is not ordinarily enlarged unless there is a complicating insufficiency of the aortic valves. Pressure of an aneurysm on the trachea may cause diminished *respiratory murmur* over both lungs. If pressure is exerted on a main bronchus, the breath sounds are diminished or absent over the affected lung.

x-Ray examination is useful as a control for other methods of examination, to follow the progress of the disease and finally to furnish definite evidence of the existence of aneurysm when physical signs fail to corroborate the suspicions aroused by the history and subjective symptoms. A *fluoroscopic examination* should be made whenever an aneurysm is suspected. This procedure should be carried out in three positions, the direct anterior, the direct posterior, and the right anterior oblique, noting in each position the contour, regularity, and density of the aortic shadow, and the presence or absence of pulsation.

Diagnosis.—It is very common to suspect the presence of aneurysm when none exists. On the other hand, an aneurysm may cause neither symptoms nor physical signs; and consequently a history of syphilis, a positive Wassermann reaction, and the presence of other stigmata of lues should be accepted as presumptive evidence that the disease has attacked the aorta, and possibly produced an aneurysm, until an attempt has been made to eliminate such a possibility by careful fluoroscopic and *x*-ray examinations.

It is not by any means always easy to differentiate aneurysm from *mediastinal tumor*, for the aorta may be obscured by the existence of an adherent pericardium, thickened pleura, mediastinal glands, or a lung tumor. In such instances, the history and the positive Wassermann reaction may be the determining factors in the diagnosis. As a rule, tumors of the mediastinum do not pulsate; but this is not an altogether trustworthy point of differentiation, for tumors may pulsate, while occasionally an aneurysm which is completely filled with fibrin does not. Tumors rarely penetrate the chest wall. Diastolic shock, a ringing second aortic sound, and an aortic diastolic murmur are signs which occur frequently with aneurysm, but are not seen with mediastinal tumors. On *x*-ray examination, it is first necessary to recognize the aortic shadows, and then differentiate them, if possible, from those of surrounding tissues. The aortic shadow as a rule is more homogeneous than the shadows of the tumors from which the aneurysm must be differentiated. An isolated tumor in the region of the aorta which pulsates, has clear, sharply-defined borders, and a uniformly opaque shadow is probably an aneurysm. An aneurysm tends to grow more slowly than do tumors of the mediastinum.

Pulmonary tuberculosis may produce certain signs and symptoms in common with aneurysm, such as cough, hoarseness, dyspnea, fever, loss in weight, hemoptysis, and a localized area of dulness on percussion, change in voice and breath sounds, and râles. A history of syphilis, a positive Wasser-

mann reaction, signs referable to the aorta, the course of the disease, and the absence of *tubercle bacilli* in the sputum serve, in most instances, to distinguish aneurysmal phthisis from pulmonary tuberculosis.

Prognosis.—The earlier in the development of aneurysm the diagnosis is made and proper treatment is instituted, the better the prognosis. In a large majority of cases, an aneurysm which has reached a sufficiently advanced state to produce signs or symptoms causes death within two and a half years, with or without treatment. Occasional cases are recorded in the literature in which patients have lived ten years or more after symptoms have developed, but such instances are distinctly unusual.

Repair, with spontaneous healing of a small sacculated aneurysm, is possible but rare. Over 50 per cent. of the cases of aneurysm of the aorta terminate by rupture of the sac. This generally takes place either into the air passages, the trachea or a bronchus, the mediastinum, the pleural cavity, or the pericardial sac; more rarely into the peritoneal cavity, into a large venous trunk, or even through the skin.

Death is caused, if not by rupture, by some intercurrent infection, such as pneumonia, or by cardiac decompensation—especially if the aortic valve is involved.

Compression of the trachea or esophagus may produce death, or the end may come with gradually developing cachexia, progressive loss in weight and strength, and increasing anemia.

Treatment of Syphilitic Aortitis and Aneurysm.—Syphilitic Aortitis.—The time to begin treatment of *syphilitic aortitis* is during the late primary stage or early in the secondary stage of syphilis. In other words, if syphilis itself is treated early, the incidence of aortic syphilis is reduced almost to the vanishing point. If one waits until the signs or symptoms of syphilitic aortitis appear, such extensive damage has already been done that the physician cannot hope to do more than relieve symptoms, or, at most, to retard the progress of the disease.

In 1910, Ehrlich described an organic compound of arsenic which had a high spirocheticidal power, with relatively low toxicity for man. *Arsphenamin* and *neo-arsphenamin*, and the more recent modifications of these compounds, have placed the specific treatment of lues on a firm basis. For the prophylactic treatment of syphilis, and for the management of the early stages of the disease, the reader is referred to the chapter on syphilis.

When symptoms of syphilitic aortitis have appeared, intensive antisyphilitic treatment should be instituted. The *drugs* which are universally employed are mercury, potassium iodid, and one of the arsenical compounds. Mercury and arsenic have definite spirocheticidal action. The iodids possess no such power, but are useful in the later stages of syphilis. Their beneficial effect is possibly due to the fact that they set free the ferments which cause autolysis of necrotic syphilitic tissue, and thus render the spirochetes more susceptible to attack by specific drugs. In order to avoid severe reactions, the so-called Herxheimer reactions, caused by the sudden release of toxins from destroyed spirochetes, a preliminary course of treatment with mercury, before the administration of one of the arsenical compounds, is advisable.

Mercury may be administered by mouth, by inunction, or by intramuscular injection. The latter method, all things considered, is the best. If a soluble preparation of mercury such as the bichlorid is chosen for hypo-

dermic use, the dose is from $\frac{1}{16}$ to $\frac{1}{6}$ grain (0.004–0.01 gm.), administered every day or every second day. If one of the insoluble salts is selected, the choice lies between the salicylate of mercury and the gray oil. The salicylate is suspended in 10 per cent. strength in paraffin oil; the ordinary dose of this preparation is 10 to 20 minims (0.6–1.3 c.c.). The gray oil is prepared according to a formula suggested by Fordyce: redistilled mercury, 30 parts; lanolin, 45 parts; olive oil, 75 parts; chloreton, 15 parts. The dose is from 5 to 8 minims (0.33–0.53 c.c.). Both of the latter preparations are put up in convenient form, in ampoules, by various pharmaceutical houses. If an insoluble salt of mercury is given, the dose suggested should not be repeated more than once a week, because it is slowly absorbed. The favorite site for the injection is in the buttocks.

While *potassium iodid* is of no value in the earlier stages of syphilis, it has a distinct place in the treatment of the later manifestations of the disease. The dose is from 30 to 120 grains (2–8 gm.) daily, in the form of a saturated solution of the drug, commencing with 10 minims (0.6 c.c.) three times a day and increasing gradually to 40 minims (2.6 c.c.) three times a day.

A course of mercury and iodids in the doses suggested should precede the administration of one of the arsenical compounds by from four to six weeks.

After such a preliminary course of treatment, *arsphenamin or neo-arsphenamin* should be administered. The initial dose should be small (not over 0.1 gm.) and should never exceed 0.3 gm. in a single treatment. The drug should not be administered more often than once a week. The contra-indications to the use of arsenical compounds are nephritis, advanced pulmonary tuberculosis, and advanced cachexia. In cardiac decompensation, arsphenamin should be used with caution.

A course of treatment consists in the administration of an insoluble salt of mercury once a week for twelve weeks, and six to eight doses of an arsenical compound, while potassium iodid is being given. Two or three such courses are given in a year, with intervening rest periods of six weeks.

The signs of improvement under such treatment are: amelioration or complete disappearance of the symptoms of syphilitic aortitis, such as paroxysmal dyspnea, anginal pain, and substernal discomfort; and improvement in the general condition of the patient. The appetite improves, the weight increases, and the blood-picture becomes more nearly normal. The Wassermann reaction does not necessarily become negative.

When *cardiac decompensation* occurs during the course of syphilitic aortitis, it should be managed precisely like cardiac failure under other circumstances.

Aneurysm.—The treatment of aneurysm, which is essentially that of syphilitic aortitis, should be carried out intensively. For the aneurysm itself, in the early stages at least, much may be accomplished by *rest—i. e.*, rest in the recumbent posture—for as long periods as ten to twelve weeks. This diminishes the rate and force of the heart and consequently reduces the volume of the sac, which in turn relieves the subjective symptoms. When the patient is finally allowed up and about, exercise must be restricted, and physical strain reduced to a minimum.

The *diet* should be restricted to the quantity sufficient to maintain the

nutrition of the individual. There is no advantage in restricting the fluid and food intake as rigidly as in the Tufnell regime.

Alcohol and *tobacco* are to be interdicted.

The various measures to *increase the coagulability of the blood* which have been suggested, such as frequent small bleedings, and the administration of calcium lactate, gelatin, etc., are of little value.

To relieve *pain* due to the erosion of bone, local applications of heat, in the form of flaxseed poultices, or an ice-cap applied directly over the seat of the discomfort may be helpful. For the more severe neuralgic pain, or the attacks of angina, morphin must be administered hypodermically, in quantities sufficient to bring relief.

Paroxysmal dyspnea may in some instances be controlled by the administration of the nitrites. If the paroxysms are repeated at frequent intervals, morphin or chloroform inhalations must be employed.

Various attempts have been made to promote *healing* in an aneurysm by the introduction of foreign bodies into the sac, in the hope of stimulating the formation of fibrin. For this fine gold or platinum wire is introduced into the aneurysmal sac, and an electric current is passed through the wire. The result of this treatment has not been sufficiently satisfactory to justify the faith that any very considerable percentage of patients can be cured or even helped by such a procedure; indeed, in many instances, it has undoubtedly hastened death.

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THROMBO-ANGIITIS OBLITERANS

Definition.—Thrombo-angiitis obliterans is an inflammatory disease of the vessels which involves the deep-seated arteries and veins and the super-

ficial veins of the extremities. In the early stages of the process a thrombus develops, which later undergoes healing and organization, causing complete occlusion of the affected vessels.

History.—The term "thrombo-angiitis obliterans" was suggested by Buerger in 1908. It is due largely to his pathological studies that the disease has been differentiated from obliterating endarteritis. Buerger's work, establishing the process as a definite clinical and pathological entity, has been universally accepted.

Etiology.—The cause of thrombo-angiitis is not known. The character of the inflammatory lesion suggests the possibility that the exciting factor may be either bacterial or toxic. *Syphilis* has been thought by some to be the etiological agent, but in a large number of published cases stigmata of lues are conspicuously absent and the Wassermann reaction is negative.

It is possible that the excessive use of *tobacco* is an important contributory factor, though in 1 per cent. of Buerger's cases its use was denied.

It is a curious fact that the disease attacks Hebrews almost exclusively, particularly those coming from central Europe; 2 per cent. of Buerger's reported cases, however, occurred in Gentiles.

Females are very rarely afflicted with thrombo-angiitis. Buerger observed but three women in his series of 500 cases.

It is a disease of young adult life and middle age and is rare in individuals more than fifty years of age. This fact helps to differentiate thrombo-angiitis from obliterating endarteritis.

Morbid Anatomy.—The vessels most commonly involved are the deep arteries and veins of the extremities. About 25 per cent. of the cases are associated with migrating phlebitis of the superficial veins.

The pathological changes in the deep vessels during the early stage of the disease can rarely be seen, but the changes in thrombophlebitis of the superficial veins are precisely similar to those in the larger and more deeply situated vessels. On gross examination, the vessels in the chronic or healed stage are found to be thickened. There is often extensive involvement of the perivascular tissue, with a varying degree of fibrosis, which causes, in extreme instances, adhesion of the artery to the accompanying vein and nerve in such a manner that they can be dissected out only with difficulty.

If an affected vessel is divided near its peripheral end, the lumen, in the early stages of the disease, is filled with a red thrombus, and the walls of the vessel are acutely inflamed. In the later stages the lumen of the vessel is occluded by a yellow or a yellowish-gray mass of organized tissue which is fenestrated. This is quite distinct from the vessel wall. If such a thrombus is traced through the course of the vessel, it will usually be found to terminate abruptly in a rounded end, although, rarely, it may occlude the lumen of the vessel throughout its entire length.

Microscopic examination demonstrates that in the acute stage of the disease, all the coats of the vessels, and often the perivascular structures, are involved in an acute inflammatory process. The walls of the vessels are infiltrated with leukocytes, and the lumen is occluded with a red clot or thrombus, in which small purulent foci are found. Later, these are replaced by connective tissue, and the mass becomes canalized with small vessels. In the late or healed stage, the arteries and veins are more or less completely occluded by connective tissue, in which new vessels have been formed, and in which pigment granules may be observed. The almost complete absence of elastic tissue in the organized clot serves as a striking point

of differentiation from obliterating endarteritis. There may be slight changes in the intima, but pronounced arteriosclerosis is observed only in the arteries of individuals who have been afflicted with thrombo-angiitis for many years, or in those who have passed into the fifth decade of life, when thrombo-angiitis attacks their vessels.

"In short, the lesions in thrombo-angiitis obliterans are, in chronological order, an acute inflammatory lesion with occlusive thrombosis, the formation of miliary giant-cell foci, the stage of organization or healing, with the disappearance of the miliary giant-cell foci, the organization and canalization of the clot, the disappearance of the inflammatory products, and the development of fibrotic tissue in the adventitia that binds together the artery, vein, and nerves" (Buerger).

Symptoms.—It is extremely uncommon for the physician to see thrombo-angiitis obliterans in its early or acute phase, largely because patients rarely seek medical advice during this stage.

The *onset* of the disease may be acute and its progress toward the advanced stage rapid; but it is more common for the onset to be insidious; the development of typical symptoms gradual; the course of the disease slow and either progressive or punctuated by periods of remission.

Thrombo-angiitis obliterans is usually first seen in the chronic or healed stage, when the manifestations are almost wholly due to impairment of the circulation by the occlusion of the deep arteries and veins in the extremities. The cardinal signs and symptoms in this stage are pain, pallor or ischemia when the limb is raised above horizontal, redness or rubor in the dependent position, and lack of pulsation in the arteries affected.

Pain is always a prominent feature of the disease. Ordinarily, it is severe and cramp-like in character, occurring in the feet or in the calves of the legs, induced by walking, and subsiding as soon as exercise is discontinued; but it may be deep-seated, entirely independent of movement, and associated with tenderness on pressure. In the later stages of the disease, when there are ulcers or fissures in the skin, or infection, or when gangrene appears, the pain becomes much more severe and constant. Phlebitis of the superficial veins, which accompanies thrombosis of the deeper vessels, is apt to be painful and often exquisitely tender on palpation. It is easy to misinterpret the cause of pain in the extremities, and until the progress of the disease points clearly to the vascular origin of the pain it is apt to be mistaken for gout, rheumatism, myositis, neuritis, sciatica, and flat foot.

Rubor or redness of one or both feet may be noticed by the patient, or may be discovered in the course of the examination. When it is constant while the foot is in the dependent position, it is called *chronic rubor*. It may, however, appear only when induced by previously elevating the limb toward the perpendicular with the patient reclining, and then depressing it below the horizontal plane. It is often necessary to repeat this procedure several times before *reactionary rubor* appears. This symptom is evidence of serious impairment of the circulation, and is due to compensatory dilatation of the superficial capillaries and venules.

Ischemia or blanching is a sign of interference with the circulation, which appears when, with the patient reclining, the limb is raised from the horizontal toward the perpendicular position. As the limb is elevated it is important to note the angle at which blanching occurs, the extent of the area involved, and the time which elapses before its appearance. After the

blanching becomes visible, and the limb is again lowered, the angle at which the color returns is termed by Buerger *"the angle of circulatory efficiency."* If blanching persists through a considerable arc, it may be assumed that the circulation is very seriously disturbed. If it persists when the limb is depressed below 90 degrees, gangrene is imminent. Blanching may take place in the toes alone, or in the entire foot, or, very rarely, in the entire limb. The greater its extent, and the shorter the time which elapses before its appearance, the greater the impairment of the circulation.

Absence of pulsation in the palpable arteries, such as the *dorsalis pedis*, posterior tibial, or even the popliteal, in the lower extremities, and the ulnar or radial in the upper, may occur early in the disease, or may be delayed until some time after the earlier manifestations have appeared. Pulsation may be present in one artery and not in another, depending upon the extent and distribution of the disease. Even extensive occlusion of arteries in the extremities may be entirely compensated for by a collateral circulation. When the larger vessels, such as the popliteal, are occluded, the symptoms referable to impairment of the circulation are likely to be aggravated.

Migrating phlebitis of the superficial veins may be one of the earlier manifestations of thrombo-angiitis obliterans. There may be no symptoms associated with its appearance, or the patient may complain of painful red spots or nodules, just under the skin, on the legs; these, when palpated, are felt as hard, more or less circumscribed, tender nodes or strands. The saphenous veins and their tributaries are more commonly involved than other veins.

Symptoms may prevail for a week or more, and then remit; the process spread along the course of the vein already involved; or, as one localized area of thrombophlebitis clears up, another focus may develop.

The later stages of the disease are characterized by trophic changes in the extremities, and gangrene. The pain is aggravated; paresthesiæ, numbness, and coldness of the limbs develop; the skin loses its normal elasticity and has a brawny, thickened texture, trophic changes take place in the nails; fissures and ulcerations form in the skin. Edema may occur in an advanced stage of the disease, immediately before the advent of gangrene.

Thrombo-angiitis obliterans may occur in vessels of the upper as well as of the lower extremities, but its incidence is much more common in the latter.

Diagnosis.—Thrombo-angiitis obliterans may be mistaken for other vascular diseases of the extremities (obliterating endarteritis) or for certain vasomotor or trophic disturbances. Many of the pitfalls in differential diagnosis will be avoided, if it is borne in mind that thrombo-angiitis, in the vast majority of instances, affects young or middle-aged male Hebrews; that the lower extremities are much more commonly involved than the upper, and usually one limb before the other; that the cardinal symptoms are ischemia, chronic or induced rubor, absence of pulsation in certain peripheral arteries, and migrating phlebitis; and that there are rarely any bony changes which can be demonstrated by *x*-ray examination.

The age incidence in *arteriosclerosis* is a decade or more later than in thrombo-angiitis; there is more general involvement of the systemic vessels; or, when sclerosis of the arteries of the extremities predominates, as in the Monckeberg type of arteriosclerosis, the well-defined beading of the palpable arteries serves as a means of differentiation; migrating phlebitis is absent; ischemia and rubor are less marked; and finally, gangrene, when it

intervenes, is apt to develop more rapidly. Calcification of the arteries may be demonstrated by the *x*-ray.

In *Raynaud's disease*, there are three stages: (1) local syncope, (2) local asphyxia, and (3) symmetrical gangrene. This disturbance attacks females rather more frequently than males. Local syncope may occur for several years in cold weather only. It is observed in the upper extremities (the hands and fingers) much more frequently than in the lower. The attacks of local syncope, during which the fingers and hands have a dead or marble-like appearance, are apt to be paroxysmal in character and of short duration. In the intervals between attacks, pulsation in the arteries returns, and there are no subjective symptoms. Cyanosis is not dependent on the position of the limb. Gangrene is symmetrical. *x*-Ray examination demonstrates marked atrophy of the bones of the terminal phalanges; eventually there may be complete absorption of a phalanx.

Erythromelalgia should not be confused with thrombo-angiitis. In the former, if the limb is allowed to hang down, the redness, heat, and pain are greatly increased; if it is held in the horizontal or raised posture these symptoms are ameliorated, but ischemia does not develop. The pulse does not disappear, but is apt to be more forcible in the dependent position. Migrating phlebitis is absent. There is often marked hyperesthesia and hyperhidrosis. Gangrene is rare.

Sclerodactyly is a rare disease which should not be difficult to differentiate from thrombo-angiitis obliterans. There are no sensory symptoms, such as pain or paresthesiæ, in sclerodactyly. *x*-Ray examination demonstrates marked atrophy of the bones of the phalanges. Edema occurs in thrombo-angiitis as a very late manifestation only.

Prognosis.—Thrombo-angiitis obliterans may be acute but is usually slowly progressive, with periods of remission when the subjective symptoms (rubor and ischemia) disappear. Pulsation, however, does not return in arteries where it has once disappeared. Relapses or exacerbations are characteristic of the disease.

Gangrene occurs as a late manifestation, and may necessitate amputation of one or more limbs. Death is eventually caused by some intercurrent disease, or by shock, or embolus as a result of the operative procedure. At best, the outlook is gloomy.

Treatment.—Inasmuch as nothing is definitely known concerning the cause of thrombo-angiitis obliterans, there is no specific remedial agent which can be utilized in its treatment. Symptoms can be relieved, however, and there is some justification for the hope that in certain instances, at least, the progress of the disease can be arrested. It will be recalled that the signs and symptoms are due either to occlusion of the deep vessels or to the effort on the part of the organism to compensate for this obstruction by establishing a collateral circulation.

The *pain* which is common throughout the course of the disease is due in the acute phase possibly to inflammation of the vessel walls, and in the later or healed stage to the diminution of the blood-supply to the muscles. Pain is increased by exercise and posture. Consequently rest and measures which improve the collateral circulation are desirable. Without regard to the stage of the disease the patient should be put to bed for a period of from four to six weeks. The horizontal posture may be sufficient to relieve the pain. Tobacco should be avoided.

The formation of a collateral circulation may be promoted by means of heat and posture. *Heat* may be employed in the form of an electric pad applied directly to the limb; or electric lights may be attached to a cradle and so arranged that the number of bulbs in active use can be regulated to control the degree of temperature. In order that full benefit may be derived from the heat, its application should be as nearly as possible continuous, or intercepted only by the postural procedures described below. *Diathermy* is said to be a valuable method of applying heat, especially in ambulatory cases. It should be given daily, at first for fifteen minutes, turning the current on slowly until the dosage is raised to 700 or 800 m. a.; this dosage may be gradually increased to 1200 m. a., for twenty or thirty minutes. *Deep light* therapy may be applied, by means of a 1000 to 1500 W. carbon lamp for ten or fifteen minutes. Heat is not well borne when thrombophlebitis exists; and if ulceration or gangrene has occurred, the part affected should be protected from direct heat. The temperature should be relatively low when the application is first made, not exceeding 120° F.: later, it may be gradually increased to 150° F., or even higher, but never beyond 170° F.

Buerger believes that *passive postural exercises* offer the best means of improving the circulation. The method employed is as follows:

"The affected limb is elevated, with the patient lying in bed, to from 60 or 90 degrees above the horizontal, being allowed to rest upon a support for from thirty seconds to three minutes, the period of time being the minimum amount of time necessary to produce blanching or ischemia. As soon as blanching is established, the patient allows the foot to hang down over the edge of the bed for from two to five minutes, until reactionary hyperemia or rubor sets in, the total period of time being about one minute longer than that necessary to establish a good, red color. The limb is then placed in the horizontal position for about three to five minutes, during which time an electric heating pad or a hot-water bag is applied, care being taken to prevent the occurrence of a burn. The placing of the limb in these three successive positions constitutes a cycle, the duration of which is usually from six to ten minutes. These cycles are repeated over a period of about one hour, some 6 to 7 cycles constituting a séance" (Leo Buerger, *The Circulatory Disturbances of the Extremities*).

The daily number of such séances must be determined for the individual.

Drugs.—Various iodin compounds would inevitably be suggested for the treatment of any vascular disease, but there is little evidence that they are useful additions to the therapeutic armamentarium in the management of this disease.

Willy Meyer believes that flushing the intestine through a duodenal tube with 8 to 10 quarts of Ringer's solution and simultaneously giving Ringer's solution by hypodermoclysis reduces the viscosity of the blood, relieves pain, and permits less radical amputation than is otherwise required.

Ulcers and gangrene must be treated surgically, with aseptic precautions. Such surgical procedures as arteriovenous anastomosis, peri-arterial sympathectomy, and ligation of the femoral vein have been suggested at various times, but, in a large proportion of cases, amputation of the limb must be resorted to, either to relieve the intense suffering or because of the advent of gangrene.

Malcolm Goodridge.

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PERIARTERITIS NODOSA

Definition.—Periarteritis nodosa is an acute or subacute inflammatory disease of the walls of the medium-sized arteries of the body. It is characterized by the occurrence of sharply localized areas of exudation, degeneration, and proliferation in the adventitial and mesial coats of the arteries affected. These changes lead to the formation of well-defined nodes, and, in some cases, to the development of aneurysms.

History.—The disease was recognized and its gross pathology described by Rokitansky in 1852. Kussmaul and Maier, in 1866, published the first gross and microscopic description of the condition, and gave the disease its name. Since Rokitansky's description, in 1852, there were not more than 70 undoubted cases reported in literature up to 1923.

Etiology.—The cause of the disease is unknown. *Syphilis* was at one time supposed to be the etiological factor, but, in the vast majority of instances, a history of syphilis is lacking, there are no other stigmata of the disease present, the Wassermann reaction is negative, and spirochetes have never been demonstrated in the lesions. The character of the inflammatory changes in the arterial walls suggests the probability, however, that some infectious agent is responsible for their occurrence.

Von Hauss, in 1920, and Harris and Friedrichs, in 1923, were apparently able to reproduce the disease in rabbits. No specific organisms have been recovered from the lesions; Harris and Friedrichs believe it to be due to a filterable virus.

The disease occurs most commonly in young adults. The youngest patient seen was three and a half years old, the oldest sixty-two. The incidence of the disease is 5 times higher in males than in females.

Morbid Anatomy.—The small or medium-sized arteries are those regularly involved in the inflammatory process, and there seems to be an especial disposition for the disturbance to attack the arteries of the heart, kidney, and gastro-intestinal tract.

Pathological changes may take place in various organs, because of the interference with their blood-supply, by thrombosis and arterial occlusion.

White or yellowish-white nodules, the size of which varies from that of a point just visible to that of a pea, may be seen in the walls of the affected artery. A node of larger size is likely to be due to the formation of an aneurysm, which may contain an organized thrombus. Infarcts and areas of anemic necrosis, which lead to occlusion, are frequently found in the lumen of the artery.

When a nodule is examined histologically, the most marked changes are apt to be in the adventitial and mesial coats. In the earlier stages of the process, the adventitia and the periarterial structures are infiltrated with polymorphonuclear neutrophiles, eosinophilic leukocytes, and a varying proportion of mononuclear cells. In a later stage, the adventitia will be seen to have undergone degeneration and fibrosis. In the media, there is early swelling of the muscle cells, inflammatory exudation of cells from the adventitia, and, finally, extensive degeneration of the media with more or less fibrous replacement.

Changes in the intima never occur without involvement of the other coats. Cellular exudation from the media and adventitia may invade the intima. The internal elastica is frequently broken or destroyed. There may be formation of hyaline substance beneath the endothelium. Proliferation of the endothelial cells may take place, with the formation of an organized thrombus, which narrows the lumen of the artery or completely occludes it.

Symptoms.—The manifestations of the disease are extremely variable. The invasion may be insidious and indefinite, or acute, with a distinct rigor. In a certain proportion of cases, there seems to be a definite relationship between infection of the upper respiratory tract and the onset, while in others the earliest indication of the disease is severe abdominal pain, referred to the epigastrium. The *fever* which is generally present is usually irregular and shows a tendency to remit. It is rarely high. The *pulse* is rapid, and the increased rate is usually out of proportion to the height of the temperature. Marked prostration, weakness, sweating, and progressive loss in weight characterize many of the cases.

As a consequence of the predilection of the disease to attack the vessels of the heart, kidney, and gastro-intestinal tract, the symptoms are likely to be referred to these regions. Thus, with involvement of the coronary arteries, evidences of myocardial disease develop; and, when the renal vessels are involved, the symptoms may be those of a subacute nephritis, with oliguria, albuminuria, and the presence of casts and blood in the urine. When the mesenteric or gastric arteries are invaded, severe abdominal pain, colicky in character, anorexia, nausea, and vomiting, or diarrhea may develop. At times, the abdominal symptoms may be of such severity that they strongly suggest an *acute surgical condition;* indeed, extension of the process into the small branches of the submucosa may result in ulceration, with perforation of the intestine and a general peritonitis. Edema of the ankles and, less commonly, of the face and body occurred in more than half the cases analyzed by Lamb. Joint and muscle pains are relatively common manifestations of the disease.

The arteries of the pulmonary field are much less commonly attacked. Asthma, cough, and hemoptysis have been reported as manifestations. The arteries of the brain are infrequently involved. In a few instances, the serous membranes have been involved, and signs of pericarditis, effusion,

peritonitis, and pleurisy have developed in consequence. Skin eruptions, often hemorrhagic in character, purpura and ecchymosis, occasionally associated with urticaria, have been observed in some cases. Small nodules, varying in size up to that of a pea, may be found in but a small percentage of cases, unfortunately, in the subcutaneous tissue of the abdomen, thorax, or extremities.

The blood-picture is that of a rather striking anemia. There is regularly a more or less marked leukocytosis, with polynucleosis and occasional eosinophilia. Blood-cultures are constantly sterile.

Diagnosis.—The disease behaves like a subacute or chronic infection, but, because of the extremely variable clinical picture, diagnosis, based upon either the history or the physical findings, is extremely difficult. Indeed, it can be made with certainty only in the rare instances when a subcutaneous node can be found and excised and submitted to histological examination.

Prognosis.—The disease usually terminates fatally within a few weeks after the onset of symptoms. In rare instances, the duration of life has been a year or more. It is said that recovery has been observed after vigorous antisyphilitic treatment.

Treatment is mainly symptomatic. Where there is a history of syphilis, or when stigmata of this disease are present, and a positive Wassermann reaction is obtained, intensive antisyphilitic therapy should, of course, be instituted.

Malcolm Goodridge.

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ARTERIOSCLEROSIS

Definition.—Arteriosclerosis is a term loosely used by clinicians to connote changes in the arteries which are characterized by hyperplasia, fibrosis, and degeneration of their walls, and are distinguished in the living subject by a variety of signs and symptoms, due to disturbances in function in the organs or other structures supplied by these arteries.

History.—Arterial disease, manifested by thickening and beading of the walls of the peripheral arteries and necrosis with calcification of the walls of the aorta, has been demonstrated recently by Ruffer and Smith in the bodies of Egyptians.

Galen, who wrote several books on the pulse, recognized that the arteries had three coats, and that the pulse was hard in some individuals and soft in others. But it was not until late in the 18th century that Morgagni indicated that the aorta was frequently involved in a degenerative process. The term "arteriosclerosis" was first used by Lobstein in 1833. The modern conception of arteriosclerosis is largely due to the work of Gull and Sutton, who, in 1872, demonstrated disease of the peripheral arteries and arterioles, with atrophy of the tissues supplied by these vessels. To this arteriolar involvement they gave the name "arteriocapillary fibrosis." Important contributions to the study of this disease, since the publication of Gull and Sutton's investigations, have been made by Mahomed, von Basch, Huchard, Thoma, Marchand, Jores, and others.

Etiology.—From the clinical standpoint, it is convenient to recognize that arteriosclerosis is commonly associated with (1) intoxication and infections, (2) old age, and (3) hypertension: but because of the very slow development of arterial changes, it is extremely difficult to prove conclusively a definite cause-and-effect relationship between infections, intoxication, senility, or hypertension, on the one hand, and sclerotic changes in the arteries on the other.

If one reviews the list of causes of arterial disease, he must be impressed at once by the multiplicity and vagueness of the factors concerned. It seems probable that certain circumstances predispose the arteries to damage, and Osler has suggested that the quality of the tubing with which one is born may influence both the incidence and the severity of the disease. Certainly, in many instances, there seems to be an inherited factor.

Typhoid fever and infections of the rheumatic type have long been known to produce changes in the arteries. Thayer found the incidence of arteriosclerotic changes much higher in those who had recovered from typhoid fever than in individuals who had not been infected and Ophüls found the condition in arteries which had been damaged by the toxins of various infections—especially those of the rheumatic type. Scarlet fever, diphtheria, and influenza have also been accused of causing similar changes.

It is possible that foci of infection, such as may occur in the teeth, tonsils, sinuses, gall-bladder, appendix, prostate, or pelvic organs, may give rise to toxins which may be exciting factors in the production of sclerotic changes in the arteries.

The association of arteriosclerosis with gout, diabetes, or Bright's disease lends suspicion to the belief that there is a well-defined relationship between the metabolic disturbance and the diseases of the arteries.

The etiological rôle of tobacco, alcohol, tea, and coffee is less probable. Indeed, there is little evidence to prove that the incidence of arteriosclerosis is higher among those who use alcohol and tobacco than among those who do not.

Old age is commonly associated with arteriosclerosis, and, while advancing years may not actually produce arterial changes, the continuous wear and tear of life may render the walls of the arteries more susceptible to change.

Marked arterial changes have been noted in the extremities of individuals who have done hard muscular work, but such labor is liable to be associated with factors which may contribute to the pathological process.

Hypertension is so frequently associated with arterial change as to lend justification to its inclusion as one of the common contributing causes of arteriosclerotic disturbances. That in itself, however, hypertension is not sufficient to cause the arterial changes is suggested by the fact that advanced chronic nephritis with marked hypertension is not necessarily associated with any change in the vessels. Some evidence justifies the belief that vascular disease and elevated blood-pressure are results of the same toxic factor, the nature of which is unknown. Inasmuch as for long periods of time the essential feature of arteriosclerosis may be high blood-pressure, the condition has been called essential hypertension or hyperpiesia.

While the incidence of arteriosclerosis is undoubtedly greater in the declining years of life, the disease is by no means rare in children.

Morbid Anatomy.—Arteriosclerosis is a general disease involving the

large and small arteries in proliferative and degenerative processes, but not necessarily to the same degree. At times, the changes are more marked in the small arteries and arterioles, the so-called diffuse hyperplastic sclerosis, while in other cases, the predominating lesions will be found in the large and medium-sized vessels. But, whether it is the large or the small arteries which are more affected, the pathological changes are essentially the same, although the process in the smaller arteries is apt to cause more diffuse proliferation in the intima, while, in the larger arteries, the changes are apt to be more patchy, and, in the type of arteriosclerosis associated with hypertension, hypertrophy of the muscular coats may be more noticeable than when the blood-pressure is not raised.

That there has been much disagreement about the nature of the pathological changes of arteriosclerosis, and the sequence in which the various coats of the arteries become involved, is not surprising when one considers the sharp differences of opinion which have existed concerning even the normal histology of the arteries. There seems to be a growing opinion that arteriosclerosis is essentially and primarily a disease of the intima, although Thoma clings to the opinion that the vessel wall loses its elasticity and undergoes dilatation with consequent slowing of the blood-stream and changes in the intimal coat. The thickening of the inner coat, which this involves, restores the dilated lumen to its normal cylindrical shape; in other words, Thoma believes that the changes in the intima are compensatory. As the disease progresses, deposits of fat appear in the cells of the intima, new connective tissue cells form, and also filaments of elastic tissue. At the same time, there may be deposits of fat in the muscle cells of the media. The tissues about the accumulations of fat undergo degeneration, cholesterin crystals appear, and calcification of the arterial wall takes place when calcium is deposited in the form of carbonates and phosphates. These changes in the vessel wall give rise to the raised yellowish patches scattered over the surface of the inner coats of the large arteries, particularly the aorta, near the orifices of the intercostal arteries. The necrotic process progresses until there is atheromatous softening, or actual ulceration with thrombus formation. Emboli from such foci may become lodged in distant arteries.

As the result of pathological changes the arteries lose their elasticity and become hard, rigid, and tortuous. Diffuse dilatation, or even aneurysmal bulging, may occur. Weakening of the arterial coats may lead to rupture. In smaller vessels proliferation of the intima may so narrow the lumina as to cause complete obliteration.

The various organs and structures whose nutrition is compromised by inadequate blood-supply may atrophy.

Symptoms.—The symptoms of arteriosclerosis depend on disturbances of the function of various structures, brought about by impairment of the blood-supply. While the disease involves the arteries of the body pretty generally, some particular organ, such as the brain, kidney, or heart, is often most affected, and the clinical manifestations may in part be attributed to localized lesions. For this reason, it is convenient to consider the disease from the standpoint of its general manifestations, and then to take up those symptoms which direct attention particularly to the brain, kidney, heart, or other structures.

General.—The onset of all types of arteriosclerosis is so insidious that in the early stages symptoms are quite apt to be entirely lacking. Under

such circumstances, the disease may be discovered during the course of a routine examination.

As the disease progresses to a more advanced stage the symptoms may be those of vague indisposition, or more distinct evidences of mental and physical deterioration, particularly in the senile type. There is gradual loss of the ability to concentrate; and in a comparatively short time the patient is no longer able to accomplish his usual mental tasks without undue effort, and, in consequence, without greater fatigue. The memory fails, particularly for recent events. The subject is irritable or depressed; lacks emotional stability; cries easily; and sleeps poorly. The appetite lags; the digestion is disturbed; the bowels become constipated; and flatulence may perhaps be a disturbing feature. There may be cramps in the muscles on exercise. There is gradual loss in weight. The skin loses its soft texture and becomes dry, thin, and wrinkled. The arteries are thickened, tortuous, hard, and often beaded, with normal or even low tension. The blood-pressure is not raised in the senile or the toxic type of arteriosclerosis, except during crises, when it suddenly rises from about 140 mm. of Hg to 200 mm. of Hg or higher. Such seizures are commonly associated with severe headache and are usually of short duration. Cardiac defeat or cerebral apoplexy may occur during such episodal crises. The chief change in the blood-pressure during senile arteriosclerosis is the low diastolic pressure; as a consequence of the normal or very slightly raised systolic pressure, and the relatively low diastolic pressure, the pulse pressure is usually greater than normal. The heart is not hypertrophied, but, on the contrary, shows evidences of myocardial inefficiency. The response to exercise is poor; there is dyspnea on exertion; and the heart sounds are of poor muscular quality.

Since the clinical picture of arteriosclerosis associated with hypertension is quite different, there has been a good deal of confusion in the minds of clinicians as to the proper classification of this disease. Mahomed speaks of it as the pre-albuminuric stage of Bright's disease; Huchard designates it as a presclerotic stage of arteriosclerosis; von Basch thought it a latent arteriosclerosis; the younger Janeway describes it as chronic hypertensive cardiovascular disease; Clifford Allbutt gives it the name hyperpiesia; and it is quite generally known in recent literature as *essential hypertension*.

Inasmuch as it seems quite probable that both the hypertension and the arteriosclerosis are due to a common factor, and in view of the fact that the chief pathological change found at autopsy is arteriosclerosis, and with full appreciation of the fact that hypertension may exist, though not commonly, without arterial change, it seems altogether simpler to include this type of arteriosclerosis under the general heading, rather than to describe it as a separate entity.

In the early stages of this type, hypertension is not accompanied by any signs or symptoms. The patients are commonly in the middle decades of life—rather younger than those with the senile type and somewhat older than those with chronic Bright's disease. They are apt to be robust, well-fed individuals, who look very healthy, and discover this hypertension by accident during life insurance or routine physical examinations.

The early symptoms may not be such as to attract the attention of the uninitiated to the cardiovascular system; indeed, they are commonly mistaken for manifestations of functional nervous disorders. Nervousness,

irritability, easy fatigability, and headache are among the early symptoms. The headache is commonly frontal, and is more apt to occur in the early morning hours. The first symptom may be precordial distress, dyspnea, or substernal discomfort on exercise.

The blood-pressure is found to be distinctly raised; systolic pressures of 250 mm. of Hg are quite common. More important than the systolic pressure is the increase in diastolic pressure, for it has been shown that as diastolic pressures increase, the arteries lose their normal elasticity and efficiency, and greater work is consequently thrown upon the heart. It is, therefore, important to bear in mind, in determining the prognosis, that those individuals whose diastolic pressures remain relatively low, in spite of high systolic pressures, are decidedly less apt to suffer from cardiac decompensation and cerebral apoplexy.

In a very short time after the onset of the hypertension, the heart becomes hypertrophied. The first sound at the apex is booming in character, and the second aortic sound is accentuated.

As the disease advances, in all types of arteriosclerosis, the symptoms are more and more apt to be referred to the structures whose blood-supply has been interfered with.

Local.—*Nervous System.*—Attention has already been drawn to certain manifestations of arteriosclerosis which indicate involvement of the cerebral arteries. The patient appreciates that he is no longer able to concentrate with his former facility, that he tires easily, that his memory is not as good as it used to be, and that sleep is no longer restful. At the same time, his associates begin to notice that his judgment is not good and that he is growing irritable and despondent. These symptoms are common to all types of arteriosclerosis in its early stages.

As the disease progresses, especially the senile type, these symptoms become more and more aggravated; the patients are restless, even delirious at night, and somnolent during the day; the memory, especially for recent events, becomes so faulty that the patient can scarcely carry on an ordinary conversation—repetitions are constant. Thromboses occur in the cerebral vessels, with consequent aphasia, dysarthria, hemiparesis, or hemiplegia; mental deterioration, covering a period of years, may culminate in dementia. Death may be delayed for years, and finally occur in coma or during a convulsive seizure.

When arteriosclerosis is associated with hypertension there may for many years be no symptoms referable to the brain; or the first sign of abnormality of the cerebral vessels may be a cerebral apoplexy. More often, the patient complains for several years of headache, frontal or occipital in location, often severe in character, and worse usually in the morning; or there occur attacks of transient aphasia, mental confusion, vertigo, or hemiparesis, of which the patient is quite conscious. These may last but a few seconds, and clear up completely, leaving no residual signs or symptoms. Such attacks have been variously explained as due to local edema, the local constriction of vessels, or claudication; but the most convincing explanation is that they are due to very small local hemorrhages. Almost invariably, such attacks are ultimately followed by severe cerebral hemorrhage. Hemorrhage into the spinal cord is much less common than into the brain, but it may occur and cause transverse hemorrhagic myelitis.

Eye Grounds.—Inasmuch as the retinal arteries are to be regarded as

branches of cerebral arteries, it is hardly necessary to emphasize the importance of a thorough ophthalmoscopic examination, and the desirability of becoming familiar with the changes which occur in the vessels of the fundi. In all types of arteriosclerosis the arteries become tortuous; there is an increase in the central light reflex; the veins become compressed at the crossings; and the walls irregularly constricted.

In the *hypertensive type*, in addition, one may find arteriosclerotic retinitis, a condition commonly mistaken for albuminuric retinitis, and characterized by the appearance of areas in the retina which are highly refractive to light and which vary in size from small specks to large, irregular patches. When hypertension exists with arteriosclerosis, hemorrhages into the retina are common. They are usually smaller and are more apt to be unilateral than in chronic nephritis.

Heart.—The symptoms referable to the heart may be due to interference with the proper nutrition of the heart muscle, because of the narrowing of the lumina of the coronary arteries; or to the development of valvular disease, secondary to the same factors which produce the changes in the arteries; or, finally, to changes in the heart muscle, which result from hypertension and increased peripheral resistance. In any event, evidences of cardiac defeat appear sooner or later, if the patient survives.

The first evidence of impairment of the heart is apt to be *dyspnea*, which develops at first on moderate exertion only, but later is produced by less and less effort; and finally, in the terminal stages of cardiac decompensation, can be observed even when the patient is at rest in bed. Dyspnea may be nocturnal in type. After a few hours' sleep, the patient is suddenly awakened with an attack of dyspnea. When this has once occurred, attacks are repeated with such regularity that patients fear to go to sleep. Dyspnea may be paroxysmal in character, the attacks coming on suddenly, like a bolt out of the blue, at times with agonizing substernal pain which causes the individual to cry out, and at times accompanied by constriction of the bronchi which produces the expiratory dyspnea and whistling breathing of bronchial asthma. Such attacks occur when the aorta is markedly involved, and are much more common in syphilitic aortitis than in ordinary arteriosclerosis.

Precordial distress is an early symptom of cardiac defeat, which may occur when there is considerable involvement of the coronary arteries or when myocardial inefficiency supervenes with little or no involvement of the coronary arteries. It may amount simply to a sense of substernal discomfort on exertion; or there may be attacks of great severity, provoked by such slight exertion as walking against the wind, overeating, or emotion.

Angina pectoris occurs quite frequently with disease of the coronary arteries. Whatever theory one may accept as to the etiology of this disease, it is generally admitted that pain in muscle can be caused by interference with the blood-supply. This is precisely what happens when the coronary arteries, which have been converted into hard, inelastic, fibrous tubes, can no longer dilate under stress and convey to the myocardium the blood necessary to meet added demands. Electrocardiographic evidence of coronary disease may be suggested by prolongation of the *QRS* interval and a diphasic *T*-wave.

Of the *cardiac irregularities* frequently observed in all types of arteriosclerosis, premature systoles are the most common. Auricular fibrillation,

which is next in order of frequency, occurs more commonly in the senile type of arterial disease than in any other. Auricular flutter and paroxysmal tachycardia are less often encountered.

One of the causes of *heart-block* may be coronary disease. *Pulsus alternans*, due to depression of contractility, is seen most frequently in senile arteriosclerosis. Sudden death may occur from thrombosis of a coronary artery.

With the advent of disease of the valves of the heart, the ordinary signs of mitral or aortic disease develop.

In all varieties of arteriosclerosis with cardiac decompensation, dependent edema and accumulation of fluid in the serous cavities may be anticipated. Sudden attacks of pulmonary edema may be observed occasionally, especially in association with high blood-pressure.

Aorta.—It is common to find at autopsy evidence of marked changes in the aorta which, during life, have produced no symptoms and no objective signs. These are usually but a part of general arterial involvement, and it may be extremely difficult to determine in a given case which symptoms are due to involvement of the aorta alone and which are due to the associated lesions in the heart, the coronary arteries, or the systemic arteries.

When the aorta is dilated dyspnea on exertion is apt to be an early manifestation, or there may be a sense of substernal oppression, which at times amounts to pain of an anginoid character and is sometimes referred to the back between the shoulder-blades. Occasionally there are attacks of paroxysmal dyspnea, but these are much more characteristic of syphilitic aortitis. Auscultatory signs are variable. There may be a systolic murmur, heard with greatest intensity to the right of the sternum and transmitted upward toward the vessels of the neck; or a diastolic murmur may appear in the same location and be transmitted down the left border of the sternum. This is to be heard with greatest intensity in the third and fourth interspaces; or there may be an entire absence of auscultatory signs. The signs elicited by observation, palpation, and percussion are generally more reliable than those obtained by auscultation. Three which are brought out by these methods of examination may occur singly or together: (1) marked pulsation of the right subclavian artery above the clavicle; (2) pulsation in the episternal notch; and (3) an increase in the area of dulness to the right of the sternum in the first intercostal space. *x*-Ray examinations are helpful in confirming the clinical findings, and also in following the progress of the disease from time to time.

Aneurysms develop occasionally in the course of non-syphilitic aortitis, but, inasmuch as the signs and symptoms differ very little from those produced by aneurysms secondary to syphilitic infection, the discussion of this complication will be taken up with syphilitic aortitis.

Kidney.—Though the kidney is involved to a very considerable extent, there may be no symptoms referable to this organ. In the early stages of the senile type of arteriosclerosis, one may find a trace of albumin and a few casts in the urine, the specific gravity within normal limits, and the function normal as determined by the ability of the kidney to concentrate and excrete sulphonephenolphthalein, nitrogen, and salt. As the disease progresses, and particularly when there are evidences of cardiac defeat and consequent passive congestion of the kidney, the urine becomes scanty, of high specific gravity, with a very large albumin content; the 'phthalein

output is greatly diminished; and there may be a very considerable retention of nitrogen. Normal function returns with cardiac compensation. In this type of renal involvement, uremic manifestations are extremely uncommon.

In essential hypertension, the patient may live for years without presenting any symptoms referable to the kidney. It is surprising to find at autopsy a shrunken kidney, not to be differentiated in any particular, macroscopically or histologically, from the small contracted kidneys of chronic nephritis, in a person who has succumbed to a cerebral accident or cardiac defeat, and who during life has shown neither subjective symptoms nor objective signs referable to the kidney. The specific gravity of the urine is within normal limits, or but slightly reduced; there is normal, or nearly normal ability to concentrate the urine; the quantity of urine passed at night is not greatly increased; there may be a faint trace of albumin, though commonly there is not; and there is no retention of nitrogen in the blood. Such a condition may persist for years (ten or fifteen) without producing any uremic manifestations whatsoever. When cardiac failure appears, as it does so commonly in this type of case, then much the same urinary and functional disturbances occur, as the result of passive congestion of the kidney, as have been described for the senile type of arterial disease. Patients in this group who escape the usual terminal events, cardiac decompensation and cerebral apoplexy, may finally develop true uremia.

Abdomen.—The symptoms referable to the abdominal viscera are much more vague than those ascribed to other structures. The attacks of severe abdominal pain have been attributed by some to vasomotor spasm, though this is pure speculation. Such indefinite symptoms as abdominal discomfort or soreness, lack of appetite, flatulence, and constipation, with progressive loss in weight, may be due to an atrophy of the pancreas and intestine, caused by interference with the normal blood-supply. It is quite likely that the repeated attacks of more or less severe abdominal pain which are occasionally observed in such cases are due to lodgment of emboli or thrombi in small branches of the mesenteric vessels. Mesenteric thrombosis, involving a main branch of the superior mesenteric artery whose anastomotic circulation is poor, causes severe colicky pain, nausea, and vomiting, shock, obstinate constipation, abdominal distention, tenderness, and finally gangrene of the intestine, peritonitis, and death.

Extremities.—The chief symptoms referable to the peripheral circulation are: (1) pain, especially in the lower extremities, which comes on during exercise, and is due to the fact that the supply of blood to the muscles is inadequate to meet the demand which the extra work entails; this pain subsides almost as soon as exercise is discontinued; (2) cramps in the muscles, which are seen usually in elderly patients, commonly occur at night, and are due either to angiospasm or, more probably, to interference with the blood-supply to the muscles; and (3) pain in the extremities, which is associated with tingling, burning, numbness, and absence of pulsation in the peripheral arteries, and with gangrene as a later manifestation. Such a syndrome is due to an obliterating endarteritis and is seen almost exclusively in the senile type of arteriosclerosis.

Diagnosis.—Arteriosclerosis can be recognized by the symptoms referable to the organs or structures whose blood-supply has been impaired, and by palpation of the peripheral arteries (the radials, brachials, and temporals)

which will be found thickened, tortuous, harder than normal, and possibly beaded. It is important to remember that tension is not raised in the type of sclerosis most apt to be associated with marked beading, or calcification, *i. e.*, the senile type. Where hypertension exists, one must differentiate between the hypertensive type of sclerosis, so-called *essential hypertension*, and *chronic nephritis with hypertension* which is commonly associated with or complicated by arteriosclerosis. This may appear to be distinction without differentiation, and, indeed, it is maintained by some authors that all nephritis is vascular in origin; but, whatever theories one may accept concerning this complicated question, it must be admitted that the clinical picture and course of so-called essential hypertension is quite different from the course and symptoms of chronic nephritis. While the pathology of the kidney, on both macroscopic and microscopic examination, in advanced stages of the two conditions, is identical, their age incidence, clinical course, prognosis, and manner of termination are quite different.

Essential hypertension occurs, as a rule, about middle age, usually in persons of robust, plethoric habit who have lived too well. The onset is insidious, discovered often by accident in the course of a routine examination; or the patient may report for examination because of slight dyspnea on exertion, frontal headache, or vague nervous manifestations. On examination, the patient looks well, his color is good, he is usually overweight, and his tension is raised, the diastolic pressure especially being high. The heart is hypertrophied. The urine is normal or contains a trace of albumin. Kidney function tests reveal no striking deviation from normal. The course is long, often fifteen years or more, and death finally occurs because of cerebral accident, cardiac defeat, rarely uremia.

This clinical picture contrasts sharply with that of chronic nephritis with hypertension. The patient is usually a decade younger, at least; and looks ill, anemic, and cachectic. The urine is of low specific gravity and may or may not contain albumin. There is marked disturbance in kidney function, as evidenced by lowered 'phthalein output, inability to concentrate, and often retention of nitrogen. The duration is shorter, death occurring in uremia within three to five years after the onset.

Obliterating endarteritis must be distinguished from *thrombo-angiitis obliterans*. When the latter is complicated by arteriosclerosis, the differentiation is not always easy. It will be helpful to remember that the age incidence of *thrombo-angiitis obliterans* is somewhat lower than that of arteriosclerosis, and that the disease occurs almost invariably in Hebrews, affects the lower extremities with greater frequency, and is commonly associated with migrating phlebitis. Blanching on elevation of the limb above the horizontal plane, with rubor on depression of the limb below horizontal, is apt to be more marked in thrombo-angiitis obliterans. While gangrene occurs in both conditions, that associated with arteriosclerosis is apt to be more acute than that occurring in the course of thrombo-angiitis.

The *x*-ray is of distinct value in determining calcification in the vessels of the extremities. It is also helpful in detecting evidences of disease of the aorta, and in controlling data obtained by clinical methods.

The age of the patient, a careful history, the presence of stigmata of syphilis in other portions of the body, the Wassermann reaction, and the *x*-ray serve to differentiate between syphilitic and non-syphilitic diseases of the aorta.

Prognosis.—Arteriosclerosis causes the death, directly or indirectly, of a large proportion of individuals who live past middle life.

A number of factors must be taken into consideration, in any attempt to predict the immediate or ultimate outcome of a given case. The type of the disease, the age, the stage of the disease, the occupation, and the presence of complications are all factors which influence prognosis.

Long life is entirely compatible with the senile type of the disease. It is common enough to see a man well past seventy with hard, beaded, tortuous arteries, who shows very little evidence of mental or physical deterioration. On the other hand, if such changes occur before middle life, the expectancy of life is greatly reduced; or if, in the senile type of the disease, complications occur, such as marked evidences of myocardial inefficiency, angina pectoris, obliterating endarteritis with gangrene, or aneurysm of the aorta, the immediate prognosis is grave.

Arteriosclerosis associated with hypertension and with good kidney function may persist for years, without producing any grave symptoms. The terminal stage in this condition is characterized by the prodromal symptoms of cerebral accident, or actual hemorrhage, cardiac defeat, evidence of impairment of renal function, and progressive loss in weight. With the advent of such symptoms, the end of life cannot be far off.

Treatment.—While, from the very nature of the pathological changes which take place in the arteries in the various types of arteriosclerosis, it is obvious that no treatment can restore the damaged vessels to their normal state, a great deal may be achieved by efforts to relieve the symptoms produced by the disturbance in function of the organs or tissues whose blood-supply has been compromised. In certain instances, it is undoubtedly possible to arrest the disease; in others, its progress may be retarded. It is in the early stages of the disease, before marked symptoms make their appearance, that efforts to stay its progress are most likely to be successful.

Certain general rules should govern the management of any of the various types of arteriosclerosis. *Foci of infection* should be removed. The *diet* should be carefully adjusted to the needs of the individual. For anemic, undernourished subjects, it may be best to prescribe a full, nourishing diet; while, for the obese, the aim should be to secure material reduction in weight. Under any circumstances, careful consideration must be given to the functional state of the digestive tract, the kidney, and the circulatory apparatus. *Tea* and *coffee* may be taken in moderation, unless their use is contra-indicated by insomnia, tachycardia, or numerous premature systoles. One of the caffein-free preparations should be substituted under these conditions.

Alcoholic drinks should be avoided, or if used should be limited to light wines taken in small quantities with meals.

The use of *tobacco* may cause palpitation, cardiac irregularity, and a rise in blood-pressure in some patients. Such individuals should discontinue its use. In any case, the use of tobacco should be restricted, and inhalation forbidden.

The bowels should be regulated by the use of the *mildest cathartics* which will accomplish the desired results.

Regular, systematic *exercise* should be prescribed, the amount and kind to depend chiefly upon the stage of the disease and the efficiency of the cir-

culation. When, for any reason, active exercise is contra-indicated, passive exercises and massage may be substituted.

Various forms of *physiotherapy*, such as warm baths, sweat baths, hot-air baths, electric-light baths, and the high frequency current, may be helpful in certain cases.

The *hours of work* should be reduced, and the *tension of life* relieved as much as possible. Long vacations should be encouraged. Sojourn in a warm climate in the winter months is desirable, but the patient, in the early or even moderately advanced stages of the disease, should not be advised to retire from business, lest the lack of interest in life which inactivity entails, may result in a loss of the will to live.

Successive generations of medical men have employed various *iodin compounds* as a routine medication in the treatment of arteriosclerosis, but, aside from tradition, and except when there is a syphilitic background, there is very little to recommend their administration. If they are to be employed at all, they should be given over considerable periods of time. The preparations most commonly utilized are the potassium or sodium salts, 0.3 to 1 gm. (gr. 5–15) in water, three times a day.

Iron and *arsenic* are undoubtedly helpful in the treatment of the anemia from which many of these patients suffer.

As a result of sclerosis of the arteries supplying the heart, brain, kidneys, abdominal viscera, and the periphery, the functions of these organs or structures are eventually disturbed, and the symptoms which are secondary to disordered function can be relieved in many instances by appropriate therapeutic procedures. When the coronary arteries are the seat of disease, the symptoms may be those of myocardial inefficiency—substernal discomfort and dyspnea on exertion; cardiac irregularities; or attacks of angina pectoris. The treatment of these manifestations of coronary disease is discussed in the chapters on the heart, cardiac irregularities, and angina pectoris.

Vascular changes in the renal arteries and arterioles may be sufficiently extensive to cause profound disturbance of the function of the kidneys, and clinical manifestations which we term uremia.

Cardiac defeat frequently causes passive congestion of the kidneys, and the development of such symptoms of renal inefficiency as oliguria, albuminuria, and edema. The treatment of these conditions has been fully discussed in the chapters on nephritis and cardiac disease.

Such symptoms as easy fatigability, failing memory, increasing irritability, depression, and emotional instability, which may be accepted as evidence of impaired circulation in the brain, should be treated by attempting to improve the general condition of the individual by regulating the habits of diet, work, and exercise.

For the hypertensive crises, with severe paroxysmal headaches, the administration of *dilators* is sometimes helpful. One may select one of the more rapidly acting members of the nitrite group, such as amyl nitrite or nitroglycerin. Amyl nitrite is dispensed in three-minim thin glass containers, which may be easily crushed in a handkerchief and slowly inhaled. Nitroglycerin may be administered by allowing a 0.0006 gm. ($\frac{1}{100}$ gr.) hypodermic tablet to dissolve on the tongue, or by dropping 1 or 2 drops of spirits of glonoin on the tongue. If the nitrites do not give speedy relief to the headache and cause material reduction in the blood-pressure, chloral in 0.3 to

0.6 gm. (gr. 5–10) doses may be tried, repeated in four hours. Since such episodal crises are quite possibly due to a toxic factor, every effort should be made to encourage elimination through the skin, bowel, and kidney. Phlebotomy, in selected cases, may be useful.

Sleeplessness and nocturnal restlessness may be relieved by the *milder sedatives*, such as sodium or potassium bromid in 1.3 to 2 gm. (gr. 20–30) doses, administered in water, twice or thrice daily. When these preparations do not produce the desired effect, recourse may be had to the *more potent hypnotics*, such as luminal, in 0.03 to 0.1 gm. (gr. ss–iss) doses. When the restlessness is extreme, or when delirium occurs, no drug is as valuable as *paraldehyd*, administered in starch water by rectum (15–30 gm.—℥ss-j); or the official elixir, containing 25 per cent. paraldehyd by mouth (15–30 gm.—℥ss–j).

Transient attacks of vertigo may be relieved by the use of dilators; or moderate doses of bromids.

Transient attacks of aphasia, paresis, drowsiness, or coma usually last for short periods and then clear up completely, without treatment. They may, however, be benefited by the same procedures which relieve the hypertensive crises.

Symptoms referable to the extremities, such as intermittent claudication and obliterating endarteritis, depend on interference with the blood-supply and may therefore be relieved by procedures which aim to improve the circulation in channels which are already operative, or to establish a collateral circulation when the arteries are occluded. The methods employed are discussed in the treatment of *thrombo-angiitis obliterans*. *Peri-arterial sympathectomy*, first suggested by Rènè Leriche, is said by him to be useful in treating painful phenomena and the trophic disturbances which lead to ulcer and gangrene. When gangrene is established, it must be treated by surgery.

The treatment of the senile or decrescent type of arteriosclerosis consists chiefly in the care of the individual and the symptoms of the disease, as they present themselves, rather than in the management of the disease as such.

In the toxic or infectious type of the disease, the conditions to which the arterial changes are secondary should be treated, in order to arrest, if possible, the progress of the pathological process in the arteries. This requires early recognition and treatment of such metabolic disturbances as gout and diabetes; the proper management of lead poisoning; anticipation of the arterial changes which may complicate certain acute infections, particularly diphtheria and typhoid; the control of intestinal intoxications; and, finally, the search for and removal of foci of infection.

In the treatment of arteriosclerosis associated with hypertension, so-called *essential hypertension*, it should be remembered that in this type of the disease, life is apt to be terminated either by a cerebral apoplexy or by cardiac defeat. Such an ending may undoubtedly be delayed by regulating the patient's life, so that no sudden stress is put upon the cardiovascular apparatus. The patient should be warned against hurry, sudden effort, lifting heavy weights, straining at stool, walking against high winds, going into the cold improperly clad, taking cold baths, over-eating, and especially against exercising directly after a meal.

Since the vast majority of these patients are overfed, plethoric, and obese, with good kidney function, it is more important that the quantity of food

be reduced than that the quality be regulated. There is little proof that either the salt or the proteid intake bears any relationship to the height of the blood-pressure. Where there is no disturbance in kidney function, a patient may be permitted an intake of 75 or 85 mgm. of protein a day, salt as it is cooked in food, and a total calory intake below the theoretical needs if the subject is above average normal weight.

In the management of hypertension itself, one must keep in mind the fact that it is the disproportionate rise in the diastolic pressure which throws the additional burden on the heart. To relieve excessive tensions, one may administer *dilators* of the nitrite group, *i. e.*, amyl nitrite by inhalation, or nitroglycerin (0.0006 gm.—gr. $\frac{1}{100}$) on the tongue, when rapid effect is desired; or sodium nitrite (0.06–0.12 gm.—gr. 1 2) or erythrol tetranitrate (0.03–0.06 gm.—gr. s̄s̄–i), to act more slowly and over a longer period of time. The quick-acting members of the nitrite group are valuable in the treatment of the pulmonary edema which develops suddenly in the course of essential hypertension.

Periodic venesection is beneficial in a certain proportion of cases of this condition.

The treatment of decompensation of the heart, kidney, and cerebral apoplexy is discussed in the chapters on the heart, kidney, and central nervous system.

Malcolm Goodridge.

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DISEASES OF THE DUCTLESS GLANDS

Diseases of the Thyroid Gland

Clinical classification:
Colloid goiter.
Adenoma.
Exophthalmic goiter.
Thyroiditis.
Myxedema.
Cretinism:
(*a*) *Sporadic.*
(*b*) *Endemic.*
Malignant disease.

The various manifestations of diseases of the thyroid gland are greatly simplified if we consider them in the light of our knowledge of the function of this organ. It serves as a storehouse of iodin and elaborates an iodin-containing substance, thyroxin, which has a controlling influence on growth and metabolism. In some manner, which we do not well understand, the thyroid affects also the other ductless glands and the autonomic nervous system.

As might be expected, disease of this gland is most frequent in districts where the iodin content of food and water is low. Such a deficiency, however, does not seem to be the only factor, as some cases appear in regions where iodin is abundant. If for any reason the iodin content of the gland falls below the normal minimum (0.1 per cent.) the organ is stimulated, its blood-supply is increased, and the cells lining the alveoli hypertrophy. Next there follows hyperplasia of the cells with infoldings which fill the spaces left by the decreasing colloid material. Often there is involution leading to complete recovery, but sometimes there is a physiological exhaustion with resulting atrophy. At times the involution may pass into a colloid stage with large masses of this material in the greatly distended alveoli (colloid goiter). Sometimes the gland does not show a tendency toward involution, but develops a greatly increased blood-supply with many infoldings of hyperplastic cells which replace the diminishing, poorly staining, iodin-impoverished colloid. As a result of this glandular stimulation hyperthyroidism develops.

COLLOID GOITER

Definition.—Diffuse colloid goiter is a diffuse symmetrical enlargement of the thyroid gland which usually starts at the age of puberty in certain inland regions where the condition is endemic. The alveoli of the gland are distended by an excessive deposit of colloid. As a rule the func-

tion of the gland is normal and the symptoms are merely due to enlargement.

Occurrence.—Goiters are common in many parts of the world, especially in certain cantons of Switzerland, in parts of England, in some districts of Africa, and in certain valleys of the Himalayas. In North America they are found chiefly in the northwest, in the Great Lakes Basin, and in the valley of the upper Mississippi. The examination of draft recruits for the War demonstrated that 21 to 27 individuals per 1000 were affected in the states of Idaho, Oregon, Washington, and Montana, while along the eastern seacoast only 2 to 5 per 1000 had simple goiters.

Etiology.—The disease was well known to the ancients, as might be expected from its striking characteristics. The association with the water-supply has long been recognized even by savage tribes, although definite proof was lacking until the brilliant studies of Marine and his co-workers showed conclusively that this form of goiter is due to a *deficiency of iodin* in the water and food. Analyses have proved that the parts of our country where the water and local vegetables contain little iodin are the very places where goiter is prevalent, sometimes so prevalent that more than half the inhabitants are affected. The same is true in the other goitrous regions of the world which have been carefully studied. Such districts are usually, but not always, rather far inland and it may be supposed that the iodin has been leached out of the soil. Near the seacoast iodin is abundant in the water and plants, and goiter is, therefore, relatively uncommon. At the present time colloid goiter may be classified as a deficiency disease, although there are some investigators who believe that infection plays a part in its etiology.

Certain it is that Marine and his associates in Ohio have been able to reduce tremendously the incidence of goiter by administering to school children small doses of iodin twice a year. Even more striking results are being obtained in Switzerland where, in some of the villages, many of the older inhabitants have enormous pendulous swellings of the neck.

Preventive treatment has been applied especially to girls, since goiter is about five times more common in females than in males. The swelling of the neck usually makes its first appearance at the time of puberty and it often tends to disappear by the age of twenty-five or thirty. There is a distinct relationship to the *sex glands* and the enlargement may increase with menstruation or pregnancy. It is particularly important that pregnant women should have a sufficient supply of iodin in order to prevent cretinism in the offspring.

Morbid Anatomy.—The thyroid gland is diffusely enlarged by this disease. It is firm and, on section, is of a reddish amber color, and contains acini distended with colloid. On microscopic examination it is found that the acini vary greatly in size, most of them being distended with normally stainable colloid. The epithelial cells are of low cuboidal shape and there may be sprig-like projections which are the remnants of previous infoldings of epithelium. Marine believes that in all of these glands there has been first a diminished iodin store, and second a period of stimulation with hyperplasia. The colloid stage is a resting phase in which the function of the gland is practically restored to normal. Adenomas are frequently found in colloid goiter causing one or more nodules. In some instances the enlarged gland presses on the neighboring organs, obstructing the trachea,

and extending downward into the thoracic cavity. The percentage of iodin contained in the goitrous gland during the resting stage may be normal, but is usually somewhat diminished. The functional ability of the gland is also usually normal, but some patients give evidence of a slightly diminished thyroid secretion.

Symptoms.—The patient or some friend first notices that there is an enlargement of the neck. Later there may be a sense of fulness and if there is pressure on the trachea, there may be difficulty in breathing during exertion. As a rule the gland is firm and symmetrically enlarged, though it may be nodular and unsymmetrical on account of adenomata. Occasionally patients are seen in whom the swelling causes a most unsightly disfigurement. Constitutional symptoms are lacking as a rule and the basal metabolism is almost always within normal limits. This type of disturbance rarely develops into exophthalmic goiter or myxedema.

Diagnosis.—Confusion is sometimes caused in diagnosis by the combination of a diffuse colloid goiter and effort syndrome (neurocirculatory asthenia) or some other nervous manifestations resembling *exophthalmic goiter*. The differentiation can be made by a careful analysis of the symptoms with especial attention to the pulse rate during complete rest or sleep. A determination of the basal metabolism is of great help. The *adenomas* can be distinguished from diffuse goiter by the palpation of nodules.

The possibility of *intrathoracic goiter* should always be borne in mind if there are any symptoms suggesting the presence of an abnormal mass beneath the manubrium.

Prognosis.—A great many goiters disappear spontaneously, and many of the others, if not too far advanced, respond to treatment.

Prophylaxis.—Preventive treatment should be used in all regions where endemic goiter is prevalent. Marine obtained brilliant results by administering to Ohio school girls at the time of puberty 2 gm. of sodium iodid (divided into 10 doses and taken during a period of two weeks) every spring and autumn. Fat tablets containing 3 to 5 mgm. of iodin flavored with chocolate may be employed, or the syrup of hydriotic acid in 1-c.c. doses daily for a fortnight twice a year. Perhaps the best prophylactic measure is the addition of sodium iodid to the table salt in districts where goiter is endemic. Such preventive treatment is particularly important at the age of puberty and during all pregnancies.

Treatment.—Marine found that during his prophylactic campaign a large number of the goiters already present in the school-girls disappeared or diminished greatly in size after the small doses of iodin had been administered. The methods described above may, therefore, be employed even though the disease has been present for some time. Boothby advises the use of *desiccated thyroid* or of Kendall's active principle of the thyroid gland (*thyroxin*). The original 5 mgm. dose (intravenous) of the latter should be followed by daily oral doses of 1.6 mgm. or by 0.15 to 0.3 gm. (2–4 grains) of desiccated thyroid. He advises controlling the dosage by determinations of the basal metabolic rate, which should be raised a little above normal. Operation is usually not necessary unless there are disagreeable pressure symptoms or adenoma.

The administration of *iodin* is not entirely without danger since it occasionally initiates hyperthyroidism when adenomas are concealed in simple goiters.

ADENOMA

Adenomatous enlargement of the thyroid gland usually causes no constitutional symptoms, but in some cases is associated with hyperthyroidism.

Morbid Anatomy.—There are in the thyroid certain tissue rests which probably represent an excess of thyroid not usually needed by the organism. These are slowly destroyed under normal conditions, but under certain stimuli react and grow. Some of these rests are of adult type, having been fully differentiated, but others are still of the fetal type. When the whole gland is stimulated by lack of iodin these fetal rests may develop into adenomata of a type which depends upon the differentiation of the cell rest at the time of the stimulus. They may pass through the stages of hypertrophy and hyperplasia and then either atrophy or by involution reach the colloid resting stage. The anatomical picture, therefore, depends upon two factors: the developmental stage of the original cell rest; and the stage of activity of the adenoma. The picture is still more complicated by the fact that the term *adenomatous growth* includes a rather wide range of conditions extending from a more or less diffuse uniform hyperplasia to a well-defined encapsulated mass. As a rule adenomas of the adult type (simple adenomas) have poorly developed capsules. The fetal adenomas, which are benign growths, are more frequently multiple and resemble large lymphoid foci. They contain no visible colloid and the stroma is scanty. An intermediate type is described between the adult and fetal. All three types of adenomas grow from a subcapsular zone, and since their blood-supply comes from the periphery, the nutrition of the central portions may be impaired. There is a tendency toward necrosis and the formation of cysts.

Symptoms.—A growing lump in the neck may be the first sign noted by the patient, but more often the growth takes place in a gland which has previously been noticeably enlarged. On examination, the mass is found to be rounded, rather firm, sometimes a little tender. Often several masses are palpable, some of them nodular on account of the fusion of several adenomata. They are not adherent to the skin or deeper structures. Sometimes the adenomata become apparent only when the enclosing mass of diffuse goiter has decreased in size as the result of treatment. Often they are discovered unexpectedly in tissue removed at operation. In most cases there are no constitutional symptoms.

Treatment.—Although most adenomas cause no symptoms other than disfigurement, it is perhaps more conservative to remove them by *operation* in order to avoid the danger of the development of hyperthyroidism and perhaps even of malignant disease. Some improve under the administration of *thyroxin*. *Iodin* should not be administered. The removal of the adenomas is not difficult and there is no tendency towards recurrence.

Plummer has called attention to a group of adenomas which cause *hyperthyroidism* usually between the ages of thirty-five and forty. The onset of the constitutional symptoms often comes without apparent cause, but is sometimes initiated by the administration of iodin, and, once started, continues even after the iodin has been withdrawn. In such cases the *heart muscle* usually shows fatty degeneration and the thymus is sometimes enlarged. The patient at the time of examination gives a history of having had a swelling of the neck for many years. There has been a gradual onset of the symptoms of hyperthyroidism with a rising *basal metabolic rate*,

which reaches an average of about 30 per cent. above normal. *Exophthalmos*, however, seldom occurs, probably because this distressing symptom is infrequent in patients who develop hyperthyroidism after the age of thirty-five. Removal of the adenoma or adenomas usually results in a rapid recovery. Plummer has called this condition adenoma with hyperthyroidism or toxic adenoma. In these cases operation should be urged unless cardiac damage has become too serious. After removal of the hyperfunctioning adenoma the prognosis is good, since the cause of the malady has been eliminated.

EXOPHTHALMIC GOITER

(Graves' Disease, Basedow's Disease)

Definition.—Exophthalmic goiter is "a constitutional disease apparently due to an excessive, probably an abnormal, secretion of an enlarged thyroid gland showing pathologically diffuse, parenchymatous hypertrophy and hyperplasia. It is characterized by an increased basal metabolic rate with the resulting secondary manifestations, with a peculiar nervous syndrome and, usually, exophthalmos, with a tendency to gastro-intestinal crises of vomiting and diarrhea. The cause of the altered pathology and activity of the thyroid gland is not known" (Boothby).

History.—Exophthalmic goiter was first described by Parry, but the published account in his posthumous writings attracted little attention and the first well-known publication is that of Graves in 1835. A few years later Basedow gave a good account of the condition. In English-speaking countries it is usually called Graves' disease and, on the continent, *Morbus Basedowi*. Moebius suggested that the cause was a pathological activity of the thyroid gland and that the disease contrasted with myxedema which is due to a loss of function of the thyroid. Friedrich Müller, in 1893, recognizing the increased protein destruction, called attention to the probability of an increased total metabolism. This was proved two years later by Magnus-Levy, who found that the oxygen consumption was above normal in exophthalmic goiter and below normal in myxedema. He later showed that the severity of exophthalmic goiter is proportional to the basal metabolism. In severe cases the metabolism is 70 per cent. or more above normal and in moderately severe cases 20 to 50 per cent. above. The determination of the basal metabolism was used but little as a clinical method until 1916, when a series of studies in America made it applicable to the clinic. Since that time there has been a marked improvement in the accuracy of diagnosis and a simplification of the literature of diseases of the thyroid.

Etiology.—Exophthalmic goiter seems to be a disease of civilization, occurring most frequently among the younger adults in cities where life is strenuous. Women are much more often afflicted than men. In a certain number of cases focal infection seems to play a rôle in the etiology, and in a much larger percentage some nervous shock or strain. Just why this should start hyperfunction of the thyroid gland is not known. Most, but not all, of the symptoms are the direct result of a hypersecretion of the thyroid. By administering thyroid extract to animals practically all of the phenomena, except exophthalmos and certain nervous manifestations, have been reproduced. Overdosage with thyroid in man has given similar results. Extirpation of the thyroid in animals and man has caused myxedema

which is the antithesis of hyperthyroidism. There is some evidence pointing towards an alteration in the nature of the thyroid secretion rather than a mere quantitative increase, and some have gone so far as to call the disease "dysthyroidism." Kessel, Lieb, and Hyman have emphasized a group of symptoms which are similar to those caused by stimulation of the thoracico-lumbar division of the involuntary nervous system.

Pathology.—The thyroid gland is diffusely enlarged, but sometimes one lobe is bigger than the other. It is soft and very vascular, and the blood-vessels are enlarged. The acini show hypertrophy, hyperplasia with infoldings of the cells filling up the space left by the greatly diminished and poorly staining colloid. The iodin content of the gland is far below normal (one-fiftieth to one-twentieth of the normal amount). The extent of the changes in the gland are not always proportional to the severity of the symptoms and in some cases the visible evidences of increased activity are slight.

In two-thirds of the severe cases there is enlargement of the thymus. A large proportion of fatal cases show mild cardiac damage, especially fatty degeneration, and in certain instances there are nutritive changes in the cervical sympathetic nerves. In one-third of the cases adenomas are also present. The heart is usually enlarged. In extreme cases there is great wasting of the body. If exophthalmos has existed for some time, there may be an increase in the retrobulbar fat.

Symptoms.—The patient's complaints are variable. Often there is an increasing sense of *fatigue*, with a nervous excitability and loss of weight. In spite of increasing weakness there may be an inward drive urging the patient to purposeless activities. An abnormal *appetite* with a sense of warmth and increased perspiration may be noticed. *Palpitation* is often the first symptom to attract the patient's attention. Sometimes an irritating cough due to pressure on the recurrent laryngeal nerve leads to the suspicion of tuberculosis. More rarely, there are no subjective symptoms until the onset of a gastro-intestinal crisis or cardiac failure.

With typical exophthalmic goiter the patient, usually a woman, has a *peculiar staring expression*, with unusually brilliant eyes, and makes many purposeless movements. On closer examination it is found that the thyroid gland is enlarged and soft, occasionally somewhat firm and nodular if adenomas are present. The gland is so vascular that the thyroid arteries may be felt and the stethoscope often reveals a whirring sound called the "*bruit de diable*." The eyes may be so protruded that a rim of white sclera is seen between the upper lid and the cornea. The lids themselves may be unduly full. The patient winks seldom (Stellwag's sign), there is a weakness of convergence (Moebius' sign), and on looking downward the upper lid follows slowly or not at all (von Graefe's sign). The cause of these peculiar ocular manifestations is not known.

There is a *fine tremor* of the hands; the *skin* is unduly warm and moist; and the *heart* beats rapidly with a slapping thrust on the chest and the sounds are of poor muscular quality. Sometimes there is distinct cardiac enlargement with relative insufficiency of the valves.

The *nervous manifestations* may be marked. A change in disposition, with unwonted irritability and unexpected losses of temper, may bewilder the family. True psychoses occasionally intervene, but as a rule the patients are easily managed once the condition is recognized. The cause of

the attacks of vomiting and diarrhea which may be alarming is not known. Involvement of the autonomic nervous system may be responsible.

Most of the symptoms are referable to increased thyroid secretion. This stimulates the resting metabolism of all the cells so that the basal metabolic rate is increased roughly in proportion to the severity of the disease. Since the oxidations are excessive even while the individual is resting, the heart must beat faster in order to supply the tissues with blood. Since the body produces more heat than normal, each square centimeter of skin must radiate an excessive amount of heat. This accounts for its warmth and perspiration. Excessive combustion calls for a greater food intake and, if the appetite is not proportionately increased, there is a loss of weight. The muscles do not seem to be as efficient as in health, and a given task is accomplished only through the expenditure of an unwonted amount of effort. It is easy to see why the continual acceleration of metabolism, night and day, exhausts the heart and causes great nervous and physical fatigue.

In severe cases of exophthalmic goiter the symptoms may develop rapidly, causing marked prostration. The basal metabolism is increased 75 to 125 per cent. above normal. The heart rate becomes very rapid, and auricular fibrillation frequently intervenes. Gastro-intestinal and nervous manifestations may be prominent. The prognosis becomes exceedingly grave and death may result from exhaustion. In moderately severe cases, when the metabolism is 40 to 75 per cent. above normal, the patient often remains an invalid for several years. The heart may be seriously damaged, and fibrillation is not infrequent. The four classical symptoms of exophthalmos, goiter, tachycardia, and tremor may not all be present, but almost invariably some nervous manifestations and the increased metabolism, with resulting rapid heart action, can be demonstrated. In mild cases of the disease, when the metabolism is less than 40 per cent. above normal, there may be a few symptoms. Such cases are often confused with neurasthenia or tuberculosis. They tend to recover spontaneously if treated by rest, but they may progress into the more severe type of the malady.

Complications.—The *focal infections* in tonsils or sinuses may demand treatment. *Acute infections* are of considerable importance since they increase temporarily the severity of the disease. *Glycosuria* occurs in 1 to 2 per cent. of the patients, being augmented by carbohydrate food. In most of these patients this is merely a spilling of sugar by the kidney, and it does not necessarily indicate a diminished power to oxidize. True *diabetes* is sometimes a complication and increases the difficulty of treatment.

Diagnosis.—Errors in diagnosis are frequent. *Early pulmonary tuberculosis* may be accompanied by nervousness, rapid pulse, and loss of weight. *Effort syndrome* (neuro-circulatory asthenia) may cause the same symptoms, with the addition of vasomotor instability. There is another puzzling group of cases with the nervous manifestations of exophthalmic goiter but without the increased metabolism. This condition has been called *"larval hyperthyroidism"* or *"forme fruste."* Its relationship to exophthalmic goiter is not yet clear. Sometimes patients with colloid goiter or adenoma are falsely suspected of hyperthyroidism. Not infrequently the clinician fails to recognize a thyrotoxic origin of cardiac failure.

In guarding against such errors there is nothing more important than

a careful history, physical examination, and analysis of symptoms. Particular attention should be given to the *pulse rate* during sleep or complete rest, since this is almost always distinctly accelerated in hyperthyroidism and not in the other diseases. A determination of the *basal metabolism* by one of the comparatively simple machines now used in many clinics is often of great value as an aid in diagnosis, but only as an aid. There are a few conditions, such as fever, leukemia, and pernicious anemia, which cause a rise in the resting metabolism similar to that of hyperthyroidism, but these are readily differentiated. As a rule the rise in the basal metabolic rate is proportional to the degree of hyperthyroidism, but it may be relatively slight in some patients whose cardiac and nervous systems have been badly damaged by a previously severe thyrotoxicosis.

Treatment.—The most important part of all treatment is *physical* and *mental rest.* This should, if possible, be obtained away from home in a place where the patient can be isolated from household cares. Sometimes this, combined with a *liberal diet*, results in a complete cure. If the body weight is to be maintained it is necessary to give about twice as many calories as are needed by a normal individual under similar conditions, since there is not only an increase in the resting metabolism but also an increase in the number of calories used for every muscular effort. It seems best to keep the protein intake low, but not so low as to interfere with the palatability of the food. The room should be cool and quiet, and all sources of excitement must be excluded. Unfortunately, there are many patients who cannot afford to stay away long from their homes and abandon the very responsibilities that have caused the malady. In such cases it is necessary either to find a more rapid method of treatment or to face the prospect of many months of invalidism.

Means and his co-workers have noted marked improvement in about two-thirds of the cases following the application of *x*-rays to the thyroid gland. If the economic status does not permit a long period of inactivity and if a skilful surgeon is available, *removal* of a considerable portion of the hyperactive gland is the best mode of treatment. The mortality of the operation depends largely on the technic and judgment of the surgeon and his assistants.

Plummer has recently been obtaining brilliant results by administering *Lugol's solution* (*liquor iodi compositus*) in doses of 1 c.c. a day for a fortnight or so before operation. This causes a rapid, temporary diminution of the symptoms of hyperthyroidism and gives the surgeon a subject in comparatively good physical condition. The patients who are very seriously ill should not be submitted to operation until the condition is improving under medical treatment. In such cases most surgeons prefer to perform a preliminary operation for ligation of the superior thyroid arteries. If the damage caused by the disease has not been too great, recovery follows operation in a considerable portion of cases. All patients who have had exophthalmic goiter must be watched carefully, as recurrences are not infrequent. If the exophthalmos has been pronounced it is usually permanent. *Gastro-intestinal crises* should be treated by absolute rest and administration of small amounts of food. Cardiac complications should also be treated by rest. Some clinicians emphasize the value of *digitalis* in large doses.

THYROIDITIS

Thyroiditis is a rare condition which ranges from a mild unnoticed inflammation of the thyroid to an acute invasion by some pyogenic organism. The tubercle never attacks the thyroid as a primary focus but may do so secondarily in a generalized invasion of the body. Infection by other organisms may follow operative interference or may spread from some neighboring structure. The disease may subside spontaneously or as a result of local applications of heat or cold. Operation is sometimes necessary, especially if obstructive symptoms intervene.

MYXEDEMA

Definition.—Myxedema is a constitutional disease, occurring in adults, and is due to decrease or absence of the secretion (thyroxin) of the thyroid gland as a result of its atrophy or removal. A marked decrease in the basal metabolic rate is characteristic as well as a myxedematous condition of the tissues, a slowed, impaired mental condition, a typical facial expression, and other secondary manifestations (Boothby).

History.—The disease as an entity was first recognized by Gull in 1873 and is sometimes given his name. Ten years later Reverdin and also Kocher found a similar condition following total extirpation of the thyroid. The latter surgeon gave it the name of *Cachexia strumipriva*. Implantation of the thyroid gland was later suggested and gave temporary relief, but the first permanent cure followed the administration of thyroid extract (Murray, 1891). Magnus-Levy discovered the low basal metabolism in 1893.

Etiology.—Myxedema invariably follows complete removal or destruction of the thyroid tissue either by operation, thyroiditis, or atrophy of the gland. It occurs sporadically and in its more severe forms is rather rare, although mild cases are probably much more frequent than is supposed. Mild grades of the disease may be found in patients with colloid goiter, and a large goiter is not incompatible with complete loss of thyroid function. Myxedema occurs four or five times as often in women as in men.

Morbid Anatomy.—Excluding the comparatively rare cases of colloid goiter, the thyroid gland in myxedema is small and atrophied. Microscopically there is a marked decrease in the vesicles and a relative increase in the fibrous connective tissue. The walls of the vesicles may show a round-celled infiltration.

Symptoms.—The onset of myxedema occurs as a rule between the ages of thirty and sixty and is very gradual. The symptom complex is in many ways the antithesis of that of hyperthyroidism. The patients, or more often the relatives, notice a gradual slowing of the mental and bodily activities, with an increased weight, a decreased appetite, and a curious change in the facial expression. In well-marked cases the expression is mask-like, the features coarse, the eyelids puffy, the hair of the head, eyelashes, and eyebrows scant. The skin is dry, scaly, and feels thick, with a curious non-pitting edema, most marked in the hands, feet, and supraclavicular fossæ. The speech is thick and slow, as the result partly of the enlargement of the tongue and partly of the delayed mental processes and the tendency toward drowsiness. As a rule the patients are placid. Quite

often they are anemic. Their joints and muscles are frequently stiff and painful. The urine may contain albumen, and the phenolsulphonephthalein test gives low results; but the blood constituents are normal and the renal function is not significantly damaged. As a rule the patients drift around for several years with a diagnosis of arthritis or obesity or nephritis before the condition is recognized and treated.

If the secretion of the thyroid is entirely absent the basal metabolism falls to a level 40 per cent. below normal. In milder cases the decrease in oxidation is proportional to the decrease in secretion. As a result of the lowered heat production the skin is cool and the patients suffer from cold. The food intake is small and there is a tendency toward obesity. In the milder forms of the disease the patient may show few typical symptoms, and in such cases a determination of the basal metabolism, which will be only 10 or 20 per cent. below normal, often gives a clue to loss of enterprise and vigor.

Treatment.—The treatment of myxedema with *thyroid extract* is one of the brilliant achievements of modern medicine. In a few weeks the patient may be almost completely restored to normal. Thyroid extract can be given at first in rather large doses until the deficit of thyroid secretion in the body has been replaced, and then given in doses just sufficient to counterbalance its rate of destruction. The various preparations of desiccated thyroid differ considerably in strength, and in certain patients they are badly absorbed from the intestinal tract.

The isolation by Kendall of the active principle of the thyroid gland, thyroxin, has made possible a method of quantitative dosage which has been worked out by Plummer and Boothby at the Mayo Clinic. They have found that there must be 12 to 14 milligrams of active thyroxin in the human body to maintain the metabolism at its normal level, and that after this amount has been accumulated, an individual with no thyroid secretion of his own must be given between 0.2 and 0.4 mgm. daily in order to compensate for the continued loss or destruction of this substance. One milligram of thyroxin given intravenously causes an average increase in the basal metabolism of about 2.8 per cent. The treatment of a completely myxedematous patient who has not previously been receiving thyroid extracts is as follows: First he is given intravenously 5 to 10 mgm. of thyroxin crystals dissolved in distilled water which is rendered slightly alkalin by 1 or 2 drops of 10 per cent. NaOH. Within twelve hours there is a reaction, with headache, nausea, pain in the back and joints, together with an increase in pulse rate, and temperature. Plummer and Boothby determine the basal metabolism daily, and as soon as the height of the curve has been reached, give a second and, if necessary, a third dose. By the end of the second week the edema has cleared, the mental conditions have improved, and the basal metabolism has reached the normal level. Then they give by mouth daily doses of 0.8 to 1.6 mgm. of thyroxin or 3 to 4 grains of desiccated thyroid. The size of the daily dose is carefully regulated by the symptoms and basal metabolism determinations and, once adjusted, this dosage serves for the rest of the patient's lifetime, although minor changes may be necessary. Individuals that are not completely myxedematous are given smaller doses. If circumstances do not permit the time-consuming procedures above numerated, the dosage may be regulated fairly satisfactorily by clinical observation.

CRETINISM

Cretinism is a disease originating during fetal life or infancy and is due to a more or less complete lack of thyroid secretion. It is characterized by a stunted physical and mental development and a typical appearance. It is not incompatible with long life.

History.—The disease has long been recognized, and dwarfs of this type have been portrayed in sculpture and painting since ancient times. It is very common in the highly-goitrous districts, and a sporadic type unassociated with goiter occurs rarely throughout the world. The relationship to the lack of thyroid secretion was recognized by Curling in 1850 and by Fagge in 1871. In fact, it was the discovery of this relationship in children which led to the recognition of myxedema in adults.

Etiology.—In regions of endemic goiter a lack of iodin in the mother's organism may cause a failure of thyroid development during fetal life or shortly after birth. This lack causes a marked arrest in the ossification of the bones, which accounts for the roentgenological picture so highly characteristic of the disease. The sporadic form probably has the same etiology as the myxedema of adults, but, occurring during infancy or childhood, causes the characteristic dwarfing of body and mind. In goiter districts there is a marked hereditary tendency, and the parents may suffer from the milder forms of thyroid disease, although adults with the more severe grades are usually sterile. In the United States the disease is relatively rare.

Pathology.—There may be a complete lack of thyroid tissue (athyreosis) or the gland may be small and atrophic as in myxedema. Sometimes a large colloid goiter is found.

Symptoms.—Usually the parents do not suspect anything wrong until the child is a year old. They then begin to notice that the infant is gaining very slowly in stature, intelligence, and bodily activities. At this time or a year or so later the syndrome becomes characteristic. The child is late in sitting up, walking, and talking. The growth, particularly in the extremities, is stunted. The skin is rough and scaly, the face bloated, the nostrils wide and flaring, with a sunken bridge of the nose, thick tongue, and drooping jaw. Dentition is delayed and imperfect, and the teeth decay early. On stripping the child one notices a pot-belly and puffy pads on the buttocks and back of the shoulders. Growth is very slow, and the intelligence much below the normal. Many cretins are unable to say more than a few words and remain uncleanly in their habits. They sit quietly for hours, responding to questions by a characteristic grin which wrinkles the whole face. Some cretins develop a clown-like intelligence and are good-humored, preserving a perpetual childhood.

Treatment.—Prophylactic treatment is all-important. In goiter districts iodin must be given to pregnant women. Recognition early in childhood is essential if we hope to attain a complete relief of symptoms. If the arrest of development has continued for a long time it may be impossible to obtain satisfactory results. *Thyroid extract* should be given in a daily dose which corresponds to 0.2 to 0.8 mgm. of thyroxin. Control of dosage by measurements of the basal metabolism is usually impossible, and the treatment must be guided by clinical symptoms. Thyroid preparations vary greatly in strength, and in some patients they are poorly absorbed.

Some cretins do well on large doses but others become distinctly ill, even on repeated attempts with smaller and smaller amounts. With or without successful thyroid medication cretins may live to old age before they succumb to an intercurrent infection.

MALIGNANT DISEASE OF THE THYROID

Malignant disease of the thyroid is fortunately rare in the United States, being found once in every 928 postmortem examinations. It is said that a correct early diagnosis is made less frequently than in malignant tumor in any other organ. The growths usually start in goiters or adenomas when the patient is between forty and sixty years of age. About two-thirds of such growths are in women.

The most common form is *Carcinoma simplex*. The growth is firm, encapsulated, and on microscopical examination there is no colloid and the alveoli form closely-packed columns of cells. This is a most malignant form, which causes metastases even though it does not penetrate its capsule. *Adenocarcinomas* contain colloid and show a tendency to infiltrate. *Papillary cystic carcinomas* grow slowly and are not always malignant. The *scirrhous* and *squamous type* are rare. *Sarcomas* may occur during the fifth and sixth decades of life.

It is difficult to distinguish between malignant growths and benign adenomas in the early stages. Malignancy should be suspected in any firm, steadily-growing tumor of the thyroid. In the later stages of malignancy there may be a stony hard mass attached to the skin and deeper structures, with a secondary involvement of the cervical lymph-nodes, or metastases into lungs, skull, or liver. There may be pressure on the trachea or esophagus. Cachexia is not striking.

The occasional development of malignancy in adenomas is an argument for operation, even if there are no suspicious symptoms. If malignancy is suspected operation should be performed early. Even then the hope of cure is small. *x*-Ray and radium treatment may help inoperable cases.

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Diseases of the Pituitary Body

Disorders of the hypophysis occur in all races and both sexes. *Acromegaly* is a post-adult[1] disease most frequent in individuals between thirty and forty years of age. It is not, however, unusual during the third decade of life. *Gigantism*, on the other hand, is a pre-adult disease, which usually begins at about the age of adolescence. It must be well established before the development of the osseous system becomes complete at the age of twenty-five. Some other disorders of the hypophysis are less rare. Their age of incidence varies according to the part of the hypophysis involved and their primary or secondary character. The onset of many posterior-lobe and bilobar (both posterior and anterior lobe) deficiencies occurs during the pre-adolescent period. Those of the anterior lobe before adolescence (Lorain-Levi type) produce *infantilism* which must begin at this time because of the characteristic resultant osseous and genital abnormalities. *Pituitary headache* occurs more often after adolescence; *pituitary polyuria* (*Diabetes insipidus*) between the second and the fourth decades; *pituitary hibernation* during the fourth decade; and *pituitary epilepsy* rarely before adolescence.

Etiology.—That *heredity* influences pituitary disorder is evidenced by the fact that in individuals with a pathological hypophysis, characteristic development and markings may be seen before the menstrual epochs, infections, trauma, or emotionalism can affect the patient. Rarely, however, is a marked pituitary disorder entirely attributable to heredity.

The *menstrual epochs* (adolescence, pregnancy, and the menopause) upset the endocrine equilibrium and consequently often involve the gland. This is particularly true in individuals potentially subject to pituitary disorders by inheritance. Gigantism usually occurs immediately after adolescence (both sexes), although a few cases are said to have been seen before that period. Acromegaly often succeeds pregnancy, because of a physiological hyperactivity of the pituitary gland. That *adolescent bilobar insufficiency* begins many years before adolescence is evidenced by the development of obesity during the pre-adolescent period. This is followed in the female by abnormal and irregular menstruation at maturity, and in the male the decreased size and function of the genitalia demonstrate this subnormal sexuality.

Pre-adolescent hypopituitarism can often be ascribed to the *acute infections* of childhood, such as measles, mumps, whooping-cough, and diphtheria. It is manifested by an initial adiposity following such diseases. While typhoid fever is sometimes considered a common exciting cause, Engelbach believes that it is comparatively rarely a fore-runner of pituitary complexes. Minor, acute infections, such as tonsillitis, bronchitis, and influenza, have been followed by rather severe pituitary disorders, but in some instances at least the patients were predisposed or showed hereditary markings of pituitarism previous to the infection. Among the *chronic infections*, syphilis is that most commonly associated with pituitary disease. The congenital type is frequently related to insufficiency of the anterior lobe (Lorain-Levi type) which produce classical *ateliotic infantilism*. Localized, basal, meningitic syphilis may cause such peculiar symptoms as

[1] Throughout this chapter it will be understood that *adolescence* occurs at about fourteen years of age; that an individual becomes *adult* at twenty-five years of age.

glycosuria, intermittent polyuria, and adiposity, during the course of an active specific disease. Gumma of the hypophysis itself is not an unusual cause of these complexes. Posterior extension of sphenoidal sinusitis occasionally disturbs the function of both the hypophysis and the optic chiasm.

Trauma—particularly of the base of the skull (fracture of the petrous portion, involving the sella turcica)—is sometimes productive of localized and general pituitary symptoms.

Such *emotional conditions* as fright, anger, etc., are thought by some observers to influence pituitary function. They are not, however, as important etiological factors as in diseases of the thyroid and adrenal glands.

Tumors of the hypophysis only rarely play an etiological rôle in pituitary disorders (less than 4 per cent. of cases, according to Engelbach).

Histopathology.—Biedl alone has attempted to relate the histology of the hypophysis to its function or the activity of its various hormones. He has recently attributed to the individual chromophil, basophil, and eosinophil cells of the anterior lobe, the functions of secreting differentiated hormones which may influence the growth of the osseous or genital systems.

Much of the confusion regarding the activity of the pituitary gland in gigantism and acromegaly is due to postmortem observations. These two clinical syndromes are in some instances associated with complete absence or destruction of the anterior lobe of the pituitary, or of the entire hypophysis, although the clinical analysis of such conditions suggests hyperplasia of the anterior lobe. Such a contradiction is probably to be explained by the fact that a neoplasm of the hypophysis produces hypersecretion during its early stage, but finally destroys the functional cells of the gland.

Pathogenesis.—The experimental work of Smith and Evans tends to prove that the anterior lobe definitely affects the growth of the osseous system and the development and function of the genital system. Their investigations also substantiate the theory that one of the important functions of the posterior lobe is the control of fat metabolism and adiposity. Isolation of the active principle of the posterior lobe (*pars nervosa* and *pars intermedia*) and determination of its effect upon the contraction of smooth muscle further confirms the idea that the posterior lobe influences the function of all involuntary muscles. It is probable that the anterior lobe exerts a similar effect on the voluntary muscles. Clinically, anterior lobe insufficiency is associated with atonicity and weakness of the voluntary muscles.

Notwithstanding the contention of most of the foreign schools, particularly the French school headed by Camus and Roussy, the best clinical, anatomical, and experimental work in the United States tends to support the above grouping system. Continental investigators have attempted to prove that nearly all the so-called general hormonic signs, such as the changes in the osseous system, adiposity, the effect on the unstriped muscle tissue, *Diabetes insipidus*, etc., are referable to lesions in the neighborhood of the hypophysis, *i. e.*, in the interpenducular region, tuber cinereum, hypothalamic region, etc. Thus far, however, the validity of this contention has not been established by either physiologists or histopathologists, and the theory that abnormal pituitary secretion, by affecting various body cells and tissues and the sympathetic nervous system, produces the symptoms, seems the more plausible. Although pituitary disorders may sometimes be related to lesions of near-by tissues, the most

convincing explanation of these changes in the regional organs and systems of the body is in the disordered function of the various lobes of the pituitary gland. The relief of such signs as polyuria and obesity by administration of the active principles of the lobes involved is corroborative.

A classification based on the functions of the individual lobes of the hypophysis is outlined in Table I. It depends solely upon the *hormonic signs*, and groups the disorders of the hypophysis into three divisions, according to whether the lobes are involved alone or together. The disorders of the anterior and posterior lobes alone are classified in groups characterized by *hypo-activity* and *hyperactivity;* those of both lobes into groups characterized by *hypo-activity, hyperactivity,* and *hetero-activity.* In the last group fall the mixed conditions in which secretory changes of the individual lobes are dissimilar. Still further subdivision is made into *pre-adolescent* and *post-adolescent,* or pre-adult and post-adult types according to the age at which the secretory state becomes abnormal. These are, finally, classified as *aneoplastic* and *neoplastic.*

TABLE I

CLASSIFICATION—DISORDERS OF THE PITUITARY GLAND

I. Anterior Lobe:	
A. **Hypo**-activity:	
1. **Pre**adolescent (*a*) A-neoplastic (*b*) Neoplastic	**Lorain-Levi Type.**
2. **Post**adolescent (*a*) A-neoplastic (*b*) Neoplastic	**Amenorrhea, Dysmenorrhea, Menorrhagia;** Loss of libido, impotence (male), reacting to anterior lobe treatment. No signs of posterior lobe disorder.
B. **Hyper**activity:	
1. **Pre**adult: (*a*) A-neoplastic (*b*) Neoplastic	**Gigantism** (no signs of posterior lobe disorder).
2. **Post**adult: (*a*) A-neoplastic (*b*) Neoplastic	**Acromegaly** (no signs of posterior lobe disorder).
II. Posterior Lobe[1]**:**	
A. **Hypo**-activity:	
1. Pars intermedia (?)	**Polyuria** (Bab) (reaction to pituitrin. Signs of anterior lobe and pars nervosa disorder absent).
2. Pars nervosa	Pituitary **obesity** (normal basal metabolism, occasionally increased sugar tolerance. Polyuria and signs of anterior lobe disorder absent).
B. **Hyper**activity	Hypophyseal **glycosuria** (normal or increased basal metabolism, decreased sugar tolerance. Polyuria and signs of anterior lobe disorder absent).
III. Bilobar[1]**:**	
A. Anterior and posterior lobes:	
(*a*) **Hypo**-activity	**Froelich's type** without, or with polyuria (Biedl).
(*b*) **Hyper**activity	**Gigantism** or **acromegaly** with **increased** basal metabolism and **decreased** sugar tolerance. Adiposity absent.
(*c*) **Hetero**-activity.	
1. Anterior lobe hyperactive. Posterior lobe hypo-active.	**Gigantism** or **acromegaly** with **polyuria.**
2. Anterior lobe hypo-active. Posterior lobe hyperactive.	**Genital aplasia, nanism, amenorrhea,** etc., with **pituitary glycosuria** (increased basal metabolism; decreased sugar tolerance).

[1] (1) Pre- and (2) post-adolescent varieties and (*a*) aneoplastic and (*b*) neoplastic types are subdivisions under each activity (hypo- and hyper-) as given under I, anterior lobe.

The distinction between hyperactivity and hypo-activity of the *posterior lobe* is not entirely clear-cut as there is uncertainty as to whether hypophyseal polyuria should be classified as an effect of insufficiency or of overactivity. This condition is perhaps best explained by Bab's theory, which attributes it to insufficiency of the *pars intermedia*. Most hypophyseal polyuria is associated with symptoms of dysfunction of either the anterior lobe or the pars nervosa. Hypo-activity of the pars nervosa without the pars intermedia produces pituitary obesity and no signs of disturbance of the anterior lobe, or polyuria. Hypophyseal glycosuria follows hyperactivity of the posterior lobe. This can be differentiated from glycosuria caused by disorder of the pancreas or other ductless glands. Although the sugar tolerance is decreased, this symptom is frequently antedated many years by polyuria and the hormonic signs of anterior lobe disorder.

The *hetero-active types* of bilobar pituitarism include gigantism or acromegaly associated with polyuria. Many patients of this hetero-active group show evidence of hyposecretion of the anterior lobe, such as infantilism, genital aplasia, amenorrhea, sexual impotence, muscular fatigue, and mental apathy, associated with such signs of hyperactivity of the posterior lobe as glycosuria, with a decreased sugar tolerance. This conception of hetero-activity may disentangle many of the so-called dystrophies which have been so ill-defined that they confuse diagnosis and treatment.

Clinical Types.—Since certain pituitary disorders are chiefly evidenced by a single distinctive sign, clinical syndromes are recognized which direct attention to the significance of these marked abnormalities and connect them with possible hypophyseal disorders. In pre-adult *hypopituitarism* of the anterior lobe, for instance, the chief complaint is *amenorrhea*. Minor deficiencies of this lobe after adolescence are usually manifested by *metrorrhea* or *dysmenorrhea*. Early insufficiencies of the posterior lobe during the pre-adolescent stage are termed *juvenile adiposity*, because obesity is the outstanding and practically the only significant sign. Hypopituitarism in later adult life causes many *constitutional symptoms*, such as headaches, visual disturbances, syncope, nausea and vomiting, constipation, and psychoneurotic manifestations. Among the purely nervous complaints, *headache*, *epilepsy*, and *hibernation* are the most important single manifestations of hypophyseal disease for which medical advice is sought.

This clinical grouping has no relationship to the anatomicophysiological classification given above. Certain clinical syndromes are, however, grouped as definite functional disturbances of one or both lobes of the hypophysis. These are: *pituitary tumor*; *pituitary amenorrhea*; *pituitary menorrhagia*, and *dysmenorrhea; pituitary adiposity*, both *juvenile* and *adult; pituitarism with marked abdominal pain; pituitarism with marked constitutional symptoms; pituitary headache* and *epilepsy; pituitary somnolence* and *hibernation; pituitary polyuria; gigantism; acromegaly; pituitary glycosuria*.

Symptoms.—The manifestations of pituitary disorder, whether neoplastic or aneoplastic, are of three types: *local*, *hormonic*, and *laboratory*. The local symptoms may be subdivided into those resulting from *local pressure*, such as deformity of the sella, ocular changes due to pressure upon the optic chiasm or tract, abnormalities in the retina or disk, and palsies of the third, fourth, and sixth nerves; pressure on the peduncles and hippocampal gyrus; and nasopharyngeal signs and rhinorrhea; and those pro-

TABLE II

HORMONIC SIGNS OF THE **ANTERIOR** LOBE OF THE HYPOPHYSIS

	HYPOPITUITARISM.		HYPERPITUITARISM.	
	Preadult.	**Postadult.**	**Preadult.**	**Postadult.**
A. Osseous.	A. **Undergrowth. All Bones. Lorain-Levi** type.	A. **Undergrowth. Short** and **flat bones** only. (Normal long bones.)	A. **Overgrowth of all bones** (Normal giant. Enunchoid giant. Acromegalic giant.) — Giantism	A. **Overgrowth. Acral, short,** and **flat bones** only. (Long bones short.) **Acromegaly.**
1. Stature: (*a*) Measurements.	1. Short: (*a*) Upper[1] greater than lower. Span less than height.	1. Tall, or normal: (*a*) Varies. Upper[1] greater than lower or less than lower (eunuchoid).	1. Abnormally tall: (*a*) Normal giant: upper = lower, span = height. Eunuchoid giant: upper less than lower, span greater than height. Acromegalic giant: upper greater than lower, span less than height.	1. Short and stocky, or normal: (*a*) Acromegaly: upper greater than lower, span less than height.
2. Head: (*a*) Sinuses. (*b*) Nose. (*c*) Superior Maxilla. (*d*) Chin. (*e*) Sella Turcica. (*x*-ray.)	Small: (*a*) Small. (*b*) Pointed, straight. (*c*) Normal. (*d*) Pointed, sharp. (*e*) Small, except **neoplastic** type enlarged.	2. Small: (*a*) Small. (*b*) Pointed, straight. (*c*) Normal. (*d*) Pointed, sharp. (*e*) Small, except **neoplastic** type enlarged.	2. Large: (*a*) Large. (*b*) Pointed, normal (eunuchoid giant). Blunt (acromegalic giant) (*c*) Normal, except prominent in acromegalic giant (*d*) Pointed, except prognathism in acromegalic giant. (*e*) Normal, except **neoplastic** type enlarged.	2. Large: (*a*) Large. (*b*) Blunt, rounded. (*c*) Prominent. (*d*) Rounded, **blunt. Prognathism.** (*e*) Normal, except **neoplastic** type enlarged.
3. Hands. (*a*) Phalanges. (*x*-ray.)	3. Type "en petite," one-third smaller than normal. (*a*) Narrow, tapering, tuberosities and tufting absent.	3. Small: (*a*) Narrow, tapering, tuberosities and tufting absent.	3. Type "en longe," one-third larger than normal. No disproportion. (*a*) Wide, dense, tuberosities large, terminal tufting, exostoses.	3. Type "en large," spade hand, wrist wide, fingers broad and clubbed. Infiltration of soft tissues over bones. Hands and head involved. (*a*) Wide, dense, tuberosities large, terminal tufting, exostoses.
4. Pelvis. (*a*) Genu.	4. Broad, feminine type: (*a*) Valgum.	4. Broad, feminine type: (*a*) Valgum.	4. Narrow, masculine type. (*a*) Varum.	4. Narrow, masculine type. (*a*) Varum.
B. Genital. 1. Gonads (ovary or testicle) and genitalia. 2. Uterus.	B. 1. Infantile hypoplasia. 2. Infantile hypoplasia.	B. 1. Normal. 2. Normal.	B. 1. Large, well developed. 2. Normal.	B. 1. Large, well developed. 2. Normal.

TABLE II (Continued)

3. Menses.	3. Amenorrhea, metrorrhagia, and dysmenorrhea.	3. Tendency to dysmenorrhea, amenorrhea, and metrorrhagia.	3. Normal.	3. Normal.
4. Sterility and Impotence.	4. Present.	4. Present.	4. Absent (present in a few years with transition to hypo-activity)	4. Absent (present after many years with transition to hypo-activity).
5. Secondary Sex Characters.	5. Absent.	5. Present.	5. Present (even after hypo-activity occurs).	5. Present (even after hypo-activity occurs).
C. Muscular.	C. Proportionate to development.	C. Normal.	C. Normal, or overdeveloped.	C. Overdeveloped.
1. Muscle Tonus.	1. Normal.	1. Fatigability frequent.	1. Loss (after few years' overactivity).	1. Retained after age of 40–45.
D. Mental.	D. Normal:	D. Average:	D. Apathetic (after activity changes).	D. Abnormally developed, temperamental, loquacious, unstable.
E. Dermal.				
(*a*) Teeth.	(*a*) Upper incisors enlarged, lateral occlusion good.	(*a*) Occasional separation and frequent enlargement of upper incisors.	(*a*) Enlarged and separated upper incisors. Lowers separated in acromegalic giant.	(*a*) Separation of upper incisors constantly; frequently of lower, with prognathism.
(*b*) Hair Distribution.	(*b*) Absent.	(*b*) Normal.	(*b*) Increase on torso.	(*b*) Marked increase on extremities and chest.
F. Temperature.	F. Subnormal.	F. Subnormal.	F. Normal.	F. Normal.
G. Pulse.	G. Slow.	G. Slow.	G. Normal.	G. Normal.
H. Blood-pressure.	H. Hypotension, or normal.	H. Hypotension, or normal.	H. Normal. Hypotension after change to hypo-activity.	H. Normal, or above normal.

[1] Upper measurement = top of cranium to symphysis (short bones).
Lower measurement = symphysis to soles of feet (long bones).

duced by *general intracranial pressure*, headache, for instance, choked disks, projectile vomiting, and photophobia. Among the *hormonic signs* some are *general*, and affect the body as a whole, changes in size, proportions, osseous development, pigmentation, growth of hair, etc.; and some are *regional*, and involve such limited portions of the body as the face, teeth, hands, mammæ, genitalia, etc. The *laboratory signs* can be determined only by special examination. They pertain to the basal metabolic rate, blood chemistry changes, the effect of posterior lobe extract upon the involuntary muscle contractions, blood-pressure, pulse rate, urinary output, etc.

Table II contrasts the hormonic signs of hypo- and hyperactivity of the anterior lobe, and Table III those produced by increased and decreased activity of the posterior lobe. That the adiposity associated with dysfunction of the posterior lobe must be due to a change in the fat metabolism and has comparatively little relation to the carbohydrate metabolism is proved by the fact that the basal metabolic rate as measured by the oxygen exchange in the lungs is normal in most patients with very marked hypophyseal insufficiency and adiposity.

Table III

HORMONIC SIGNS OF THE POSTERIOR LOBE OF THE HYPOPHYSIS

	*Hypo*pituitarism	*Hyper*pituitarism
I. Adiposity:	I. Marked girdle, mons and mammary:	I. Absent, usually emaciation:
(*a*) Basal metabolism.	(*a*) Normal, usually.	(*a*) Normal (usually).
(*b*) Carbohydrate tolerance.	(*b*) Normal, usually.	(*b*) Decreased.
(*c*) Glycosuria and hyperglycemia.	(*c*) Absent.	(*c*) Present.
II. Involuntary Muscle contraction:	II.:	II.:
(*a*) Intestinal.	(*a*) Absent; frequent intestinal atony.	(*a*) Present; frequent intestinal spasticity.
(*b*) Uterine.	(*b*) Absent.	(*b*) Present.
III. Polyuria.	III. Present (pars intermedia?).	III. Absent (or present with glycosuria).
IV. Endocrine secretion:	IV.:	IV.:
(*a*) Thyroid.	(*a*) Hypo-activity (hibernation).	(*a*) Hyperactivity.
(*b*) Adrenals.	(*b*) Insufficiency?	(*b*) Hyperactivity?
(*c*) Gonads.	(*c*) Hypo-activity (with anterior lobe disorder).	(*c*) Hyperactivity (with anterior lobe disorder).
(*d*) Pancreas.	(*d*) Normal (occasionally increased sugar tolerance).	(*d*) Hypo-activity (decreased sugar tolerance).
V. Nervous.	V. Apathy; somnolence frequent.	V. Psychic instability.
VI. Temperature.	VI. Subnormal.	VI. Normal.
VII. Pulse.	VII. Slow.	VII. Rapid.

Hypophyseal Tumor.—Tumor constitutes a part of the pituitary syndrome in less than 4 per cent. of clinical cases. The characteristic local signs of neoplasm of this gland are merely superposed on the general hormonic picture. In the great majority of pituitary disorders (95 per cent.) the pituitary neoplasms are absent, and, consequently, the classical

symptoms of local and general intracranial pressure do not develop. Such signs as migraine and various other types of headache, psychic and mental disturbances, and vague, subjective, ocular symptoms are, however, sometimes mistaken for definite signs of hypophyseal enlargement, and for this reason pituitary tumors are described in some detail as the first clinical type of pituitary disease.

Deformity or erosion of the sella turcica is the one sign constantly suspected in any syndrome which may be referable to the hypophysis, but the normal variations in size must be considered. The maximum measurements of Keith (9 x 14 mm.) and of Cushing (10 x 15 mm.) for a normal sella turcica are in general correct, but considerable allowance must be made for differences in the size of the skull. A diagnosis of neoplasm of the hypophysis depends not only on unquestionable enlargement of the sella, but also on local pressure signs. The so-called imprisoned sella, in which the anterior and posterior clinoid processes apparently encroach upon each other or are closely approximated, is often considered to be abnormally small, and held responsible for many functional changes in the gland. An anatomical study of the pituitary fossa, however, demonstrates that it is really not modified by the position of the clinoid processes. The anterior and posterior clinoid processes may apparently be approximated on the *x*-ray plate and yet produce absolutely no impingement on the infundibulum or the gland itself. While an unusually large or eroded sella is the best single evidence of pituitary tumor, it is necessary to realize that neoplasms can develop without modifying the normal size and shape of this bony saddle. This occurs in the early stages when some of these tumors grow directly upward or laterally below the clinoid processes. In the majority of cases, however, there will appear at some time a deformity of this bony structure.

The belief that bitemporal hemianopsia is a necessary accompaniment of hypophyseal tumor has been so prevalent that oculists and neurological surgeons have not appreciated that it is a rare sign of these tumors. The perimeter defects resulting from hypophyseal neoplasms vary so much from this classical type that they are more often attributed to some such benign condition as hysterical blindness, toxic amblyopia, or secondary infection from focal disease in the sinuses or teeth, rather than to a localized pressure upon a limited number of fibers of the optic chiasm or tract. Pituitary neoplasms may produce a transient, fleeting blindness, initially asymmetrical, the location of which varies at different stages of the disease. This is the most constant ocular symptom due to these tumors. Retinal blindness resulting from direct pressure or dragging upon the optic chiasm or tract rarely produces typical temporal hemianopsia. The degree of amaurosis depends on the location of pressure and the direction of growth of the tumor. When the growth is directly anterior and presses upon the chiasmic fibers exactly at their crossing, classical hemianopsia in the temporal fields results. It is more usual, however, for pressure to be exerted on the mesial fibers of one optic tract, and thus produce a unilateral defect at the perimeter. Later, the tumor may not infrequently decompress itself either through the posterior wall of the sphenoid sinus or by eroding the posterior clinoid process. This releases the pressure which has been exerted upon certain points of the optic nerve, and consequently temporarily relieves the retinal blindness. Still later the tumor may grow until it again involves the same portion of the nerve and thus recalls or extends the original blind-

ness. There are many variations of these classical defects of the visual fields, and changes are found to be unilateral as often as bilateral. Homonymous deviations are almost as frequent as bitemporal hemianopsia. The other ocular signs, such as diplopia, choked disk, optic atrophy, and ocular palsy, are of less significance than the perimeter deviations in the diagnosis of these tumors. The third, fourth, and sixth nerves are rarely involved, and when they are, it is usually only in the very late stages of an unusually large tumor. Choking of the disk is one of the signs of general intracranial pressure, and is frequently superposed on a primary optic atrophy produced by direct pressure on some portion of the optic nerve. Pupillary irregularity is an infrequent sign. Disturbances in gait due to ataxia result from such lesions. These, as well as the nasopharyngeal signs (decompression of the tumor into the pharynx, rhinorrhea, or discharge of cerebrospinal fluid through the nose or pharynx), develop late, and should not be anticipated. In fact, they should be considered more as late complications than as early diagnostic signs.

Although headache is the most common sign of general intracranial pressure, it may in exceptional cases be absent throughout the entire course of a pituitary neoplasm. Projectile vomiting, photophobia, and choked disk are associated with large tumors of the hypophysis with the same relative frequency as other diseases of intracranial pressure. To these local and general symptoms of intracranial pressure may be added any one or a number of the hormonic signs according to the lobe or lobes involved and the age at which the disorder occurs.

Clinical Syndromes Resulting from General Hormonic Signs.—The following pituitary syndromes are due to the effect of the hormones of the different lobes on the various systems and organs of the body. They are purely functional disturbances of the hypophysis and are not related to pituitary neoplasm. As has been stated, pituitary tumors may often be associated with hormonic manifestations, but in the clinical types to be described there need be no evidence of local or intracranial pressure. Except in the case of pituitary headache and epilepsy, the predominating changes or symptoms affect distant organs and tissues of the body. The names of the syndromes are derived from the chief symptom which predominates to such a degree that it obscures other signs of pituitarism. Nevertheless, there are in nearly all these syndromes signs referable to other systems, which indicate that the pituitary function is disturbed. These make diagnosis certain.

Pituitary amenorrhea is a sign of insufficiency of the anterior lobe of the hypophysis and occurs most typically in the Lorain-Levi variety of disorder. Amenorrhea, partial or complete, is also a sign of bilobar pituitary insufficiency (Fröhlich's disease). The diagnosis of complete pituitary amenorrhea depends on a marked retardation of osseous growth and development, combined with aplasia of the gonads. The clinical proof that the posterior lobe is not hypo-active in this disorder consists in the absence of girdle adiposity and pituitary polyuria (*diabetes insipidus*). The marked retardation of osseous growth and development is demonstrated most vividly by a relative undersize of all the bones of the body—classical infantilism. These observations may be supplemented by *x*-ray examination of the osseous system, which demonstrates the delayed epiphyseal closure existing with the typical undeveloped long and short bones. Fusion of the epiphyses takes place three or four years later than normal,

but in spite of this retarded union, which is usually associated with a marked increase in the long bones, there is no increase in height or size in these individuals. This striking undergrowth of all the bones, when the epiphyses remain open longer than normal, provides a specific means of diagnosing these cases by *x*-ray studies: and also permits differentiation of the amenorrhea due to primary ovarian insufficiency, which is also associated with very late fusion of the epiphyseal ends of the long bones. In hypogonadism or eunuchoidism instead of a retardation of the growth of the long bones there is an overgrowth produced by the hormone from the anterior lobe of the hypophysis. The peculiar osseous development which follows the absence of anterior lobe activity results in a disproportionate stature, the upper measurement (symphysis to top of head) being greater than the lower (symphysis to soles of feet). Pituitary insufficiency relatively increases the upper measurement and eunuchoidism the lower. Other diseases which retard osseous growth and produce aplasia of the genital system (nanism, chétivism, nanism complet, etc.) must be differentiated by the individual signs. All types of infantilism due to lesions of other systems, such as mitral stenosis, tuberculosis, alcoholism, and saturnism, can be easily distinguished from true pituitary amenorrhea by the lesions in the systems involved or by the history. The retarded growth of the cretin is very easily recognized by the markedly low mentality characteristic of severe hypothyroidism. This is absent in all simple, uncomplicated forms of pituitarism. In some other types of dwarfs, such as Lilliputians, Falta's type, rachitic dwarfs, and achondroplastic individuals while the genitalia are somewhat undeveloped, there is usually no loss of genital function. Mongolism and moronism can be recognized by the low mentality.

Pituitary menorrhagia and dysmenorrhea are due to partial insufficiency of the anterior lobe. Occasionally these menstrual symptoms begin at maturity, but more often not until a number of years after adolescence, in the course of normal menstruation. The diagnosis may be made by other signs of pituitary disorder (osseous, orthodontial, *x*-ray, etc.) and by relief of the dysmenorrhea or menorrhagia which follows administration of anterior lobe pituitary substance. If such therapy in large oral and hypodermic doses does not relieve the menstrual disturbances, diagnosis cannot be positive.

Pituitary Adiposity.—Two types of obesity are associated with pituitary insufficiency—the juvenile and the adult. They are separately classified on account of the prevalence of juvenile adiposity and the importance of treatment before adolescence in order to prevent other serious disorders resulting from the abnormal genital development which follows anterior lobe insufficiency. Adult pituitary obesity is usually part of a bilobar insufficiency (Fröhlich's syndrome), although in a few instances insufficiency of the posterior lobe alone, without involvement of the anterior lobe, is present. In from 70 to 80 per cent. of the juvenile obese, deficiency of the posterior lobe of the hypophysis plays an etiological rôle. Juvenile adiposity frequently follows childhood infections and is occasionally superposed on such other endocrine disorders as partial congenital hypothyroidism. Pituitary obesity rarely develops before the fourth or fifth year of life. Overweight at birth is more likely to be due to hypothyroidism than to other endocrine disorder. The obesity due to hypogonadism is uncommon before adult life. Even that produced by early castration is

restricted to an area of a few inches in the trochanteric region of the thigh. Further proof that such pre-adolescent obesity is almost always due to the hypophysis can be found in the fact that most of such conditions respond to substitution treatment with preparations of the posterior lobe. This pre-adolescent obesity is *per se* of only relative importance because it produces little incapacity, but if improper development of the genital system due to associated or secondary insufficiency of the anterior lobe of the hypophysis is to be prevented, this condition must be suspected a few years before adolescence. Since juvenile adiposity is suggestive of this, and may indicate the necessity of prophylactic treatment to counteract the decrease or loss of function of the anterior lobe, it assumes diagnostic importance.

Obesity which develops in the third and fourth decades may result from one of three endocrine causes—hypothyroidism (myxedema), hypogonadism, and hypopituitarism, or a combination of two or three of these disturbances. It is very rare, however, for a markedly rapid accumulation of panniculus adiposus to occur before the age of twenty-five in any condition except hypopituitarism. After adolescence it is usually a manifestation of bilobar insufficiency. Most female patients present many signs referable to the anterior lobe, in addition to the obesity and other evidences of posterior lobe deficiency. It is true, however, that not all cases of juvenile, early adult, or even late adult adiposity result from pituitary, or other endocrine dyscrasia. Biedl, for instance, has described a case of cerebral adiposity associated with a marked mental retardation and a retinitis pigmentosa. The most characteristic and easily recognized sign of bilobar pituitary insufficiency is this typical girdle adiposity which involves the hip more than the shoulder girdle, and is associated with diminished function of the genital system. It is seen in the female more than in the male. The anterior lobe insufficiency is evidenced by menstrual changes, varying from a slight decrease in the menstrual flow to an amenorrhea of months or years. A tendency to amenorrhea combined with a very rapid gain in weight in the girdle region is very positive evidence for a diagnosis of anterior lobe deficiency. The adult obesity most frequently follows menstrual epochs, particularly the first or second pregnancy, more noticeably in certain races, as the Hebraic. It is also a sequela of various focal or general infections, and rarely of cranial trauma and emotionalism. This type is distinguished from adiposis dolorosa by the fact that the fatty tissue is more evenly distributed and is accentuated in the girdle region. The irregular, painful tumor masses present in Dercum's disease are absent. The condition is often complicated after a few years by a secondary hypothyroidism, with extension of the adiposity to the supraclavicular region and the backs of the hands and feet: the panniculus infiltration also tends to become more or less diffuse over the entire body.

Pituitarism with Marked Abdominal Pain.—Post-adolescent or post-adult bilobar insufficiency of the hypophysis with pain in the right inguinal region is frequently mistaken for appendicitis or adnexal disease. Pain in the right inguinal region often definitely localized over McBurney's point so dominates the syndrome in this type of pituitarism as to tend to obliterate other signs of the disturbance. This symptom is so constant and distressing that many patients finally undergo operation, usually first for appendicitis and later, when this proves useless, for adhesions or pelvic

lesion. The condition can be differentiated from recurrent appendicitis, however, by the absence of such signs of infection as chills, fever, and leukocytosis. There are rarely reflex symptoms, such as nausea and vomiting. The pain is consistently localized from the onset in the region of McBurney's point and never begins, like that of acute suppurative appendicitis, as a diffuse abdominal or epigastric pain which later localizes over McBurney's point. It is usually intensified at the menstrual period and associated with other signs of dysmenorrhea, like backache, cramps, and headaches. Nearly always, however, it is present, although less intense, throughout the interval between periods.

Pituitarism with Marked Constitutional Symptoms.—Insufficiencies of the hypophysis associated with numerous constitutional symptoms occur in the post-adult age. Some patients, who were normal until the age of twenty-seven to thirty-two, begin to menstruate irregularly, amenorrheal intervals of three or four months' duration being associated with a sudden gain in weight about the girdle region. Many other symptoms appear with these signs of hypopituitarism, such as migrainous headaches, various ocular symptoms (difficult to relieve by correction of errors of refraction and other local treatment), nausea and vomiting, tachycardia, intermittent paroxysmal dyspnea, sensation of fulness in the abdomen, constipation, and dysmenorrhea. Indeed the symptoms are so heterogeneous that they are ordinarily considered psychogenic or the result of various local lesions of the cranium, eyes, cardiovascular system, or gastro-intestinal tract.

Pituitary Headache and Epilepsy.—Pituitary headache is very severe, although not characteristic in localization or type. In the majority of patients it is more or less migrainous in nature, and accompanied by various ocular and gastric disturbances. Occasionally, simple ocular symptoms with pain restricted to the frontal region, affecting only one eye (migraine ophthalmique), associated with no other cranial symptoms or nausea, occur. Hemicrania is not a sign characteristic of this condition, and the pain is located frequently around the base of the skull, and in the lower temporal regions, posterior occipital region, and posterior orbital region. The diagnosis of pituitary headache depends on the presence of other signs of pituitarism and the marked relief of the symptoms by pituitary therapy. In exceptional cases, preparations of the anterior or posterior lobe actually increase the headache, probably because an existing hypersecretion of one lobe is intensified by administration of more of the hormone. The classical pituitary headache is associated with hyposecretion and is relieved very satisfactorily by administration of substance from one or both lobes.

Pituitary epilepsy has long been described by neurologists as uncinate epilepsy. It is a comparatively rare type, for probably less than 5 per cent. of all epilepsy results from disorder of the hypophysis. It is evidenced by uncinate or hippocampal gyrus signs referable to perversions of the olfactory or gustatory sense. During the aura or following the epileptic attack there is usually some marked abnormality of the sense of smell or taste, which, with other pituitary signs or symptoms, should suggest the true nature of the epilepsy. Diagnosis is definitely confirmed by relief for more than five years following pituitary treatment. Relief for many months or a year or two at a time is not significant because the intervals between attacks of pituitary epilepsy may be long.

Pituitary Somnolence and Hibernation.—Pituitary hibernation and somnolence result from hypo-activity of both lobes of the hypophysis and occur in the late post-adult age. Probably, however, this condition is not produced by hypopituitarism alone, but becomes marked only when there is secondary hypothyroidism. Such deductions are confirmed by comparison of the response to pituitary and thyroid treatment separately with that to combined thyropituitary therapy. In so-called pituitary hibernation, pituitary treatment alone, like thyroid therapy alone, produces only partial relief. Neither serves to cure completely, but a combination of the two restores a very large proportion of patients to normal.

The symptoms are those of mild or pronounced somnolence, which in some instances becomes so severe that the patient can be aroused only with difficulty. With this condition, there are other signs of insufficiency of both lobes of the hypophysis, as well as minor manifestations of thyroid insufficiency.

Pituitary polyuria has been thought by Bab to be attributable to hyposecretion of the pars intermedia. Practically 50 per cent. of patients react to pituitary treatment more or less satisfactorily, those with decided pituitary markings showing the best response. About 50 per cent. of the patients in the author's experience who seem to have the classical syndrome of diabetes insipidus with few osseous, orthodontial, genital, or obese signs of pituitarism, are much less affected by pituitary treatment.

The three syndromes, *gigantism*, *acromegaly*, and *pituitary glycosuria*, follow hyperactivity of the hypophysis, gigantism and acromegaly being due to hyperactivity of the anterior lobe in the pre- and post-adult ages respectively, and pituitary glycosuria to hyperactivity of the posterior lobe. Although giantism and acromegaly have formerly been associated by physicians with pituitary neoplasm, a considerable number of both acromegalics and giants present absolutely no signs of pituitary tumor: in these individuals, the hyperactivity of the anterior lobe must be due to other causes.

Giantism (*Gigantism*).—Falta defines giantism as a condition in which the height is more than 79 inches (200 cm.). He divides giants into three types: (*a*) the *normal* with the upper measurement equal to the lower, and the span equal to the height; (*b*) the *eunuchoid* with a longer lower than upper measurement without signs of hypogonadism in the genital system; and (*c*) the *acromegalic* with changes in the short and flat bones as well as marked overgrowth of the long bones. Recent authors have been inclined to attribute giantism to hypersecretion of several ductless glands, thus making it the antithesis of pluriglandular sclerosis, or insufficiency of a number of ductless glands. The more general belief, however, is that the cause is hypersecretion of the anterior lobe of the hypophysis, which involves other endocrine disorders. The osseous and genital manifestations are related to the anterior lobe, the hyperactivity of which produces the marked overgrowth of the bones, most frequently during or following the age of maturity. The initial rapid growth rarely takes place before adolescence.

Most normal and eunuchoid giantism is evidently due to simple functional hyperactivity of the anterior lobe of the hypophysis, and is nearly always aneoplastic. Acromegalic gigantism, on the other hand, is usually associated with pituitary neoplasm. In normal giants there is not so marked a tendency to subsequent mental retrogression or to a loss of general muscle tone; in fact, a great many retain unusual mental activity, muscular tone,

and genital function until late in life. The eunuchoid giants, as well as the acromegalic giants, however, are subject to transition from a hyperactivity to a hypo-activity of the pituitary during the early course of the disease. This reversion of activity is accompanied by general muscular weakness, mental disability, loss of libido and potency, and other signs of mental and physical decline.

Acromegaly results from hyperactivity of the anterior lobe of the hypophysis in the post-adult age, after the epiphyseal ends of the long bones have become inactive. The overgrowth is, therefore, confined to the short and flat bones and the muscular and dermal systems. The characteristic blunting of the peaked bones and the mushrooming and hooking of the terminal phalanges are the chief objective signs of this disorder. There is a general enlargement of the head, prominence and rounding of the chin, thickening of the lips, and enlargement and fulness of the nose and malar eminences, causing an apparent posterior displacement of the ear due to the increased forward growth of the bony processes. *x*-Ray photographs of the head show increase in the size of the sinuses, thickening of the skull, and overgrowth of the frontal, malar, and occipital protuberances. The concomitant changes in the vertebræ tend to effect a kyphosis of the upper thoracic vertebræ and a turtle-like posture of the neck and head. The other bones simultaneously involved are those of the hands and feet. This regional enlargement and growth is so rapid that during the acute stage the patient needs a larger pair of shoes or gloves every few weeks. The soft parts of the face, hands, and feet become thickened and hypertrophic, and the extreme localized hyperhidrosis is evidence of the hyperactivity of the skin. The shape of the hand changes from normal to the "spade" type with a very short, wide wrist, sausage-shaped fingers, and nails apparently buried by the soft tissues. *x*-Ray examination of the hands and feet demonstrates that the individual bones are abnormally wide, thick, and dense, and that their tuberosities are prominent. The tufting or mushrooming of the terminal bones of the fingers and toes augments the clubbing of the ends.

Various musculo-osseous pains occur during the active stage of acromegaly, and are confused with those of such common conditions as arthritis, neuritis, and neuralgia. The hyperactivity of the anterior lobe is much more prolonged in acromegaly than in giantism, often persisting for fifteen to twenty years, and even until the patient attains the age of sixty or seventy. In acromegalic individuals, without tumefaction of the hypophysis, the activity demonstrated by the increase in mental capacity, muscular power, and sexual continence frequently continues until after the sixth decade.

In both giantism and acromegaly there are orthodontial changes due to enlargement of the malar prominences. This change in the arch of the mouth effects more or less definite separation of the teeth, and the overgrowth of the inferior maxilla, the characteristic prognathism. Among the general hormonic signs of acromegaly is the abnormal bodily proportion produced by the elongation of the upper measurement as compared with the lower. The characteristic hypertrichosis, which affects the extremities and torso particularly, is contrasted in later life with a frontovertical alopecia. This differs somewhat from the hair distribution in giantism, in which there is less tendency to hypertrichosis of the terminal extremities and to vertex alopecia. The chloasma which has recently been considered

in part due to the anterior lobe occurs in both sexes, but more often in females than in males. The discoloration is confined to the forehead, angles of the mouth, lateral aspects of the neck, and nipple regions. In exceptional cases it diffusely covers the entire face, neck, and arms with contiguous patches of vitiligo.

Pituitary Glycosuria.—Hypophyseal glycosuria is a condition of hyperglycemia and glycosuria which is associated with hypersecretion of the posterior lobe of the pituitary. Concurrent signs and symptoms of hyperactivity of the hypophysis confirm the etiology. Glycosuria is not uncommon during the early stages of pituitary tumor. Pierre Marie stated in his early reports (1886–87) that in 30 to 50 per cent. of cases of acromegaly there was glycosuria, and Borchardt states that glycosuria occurred in 35 per cent. of acromegalics. Von Noorden emphasizes the striking independence of the sugar content of the diet. Oppenheim reported glycosuria in a considerable percentage of cases of basal meningitis and attributes it to involvement of the hypophysis.

The hyperglycemia is unrelated both to the glycosuria and to the carbohydrate intake. In one of the writer's patients, the blood-sugar was very high while there was no sugar in the urine. A few weeks later there was glycosuria, and the sugar content of the blood was comparatively low and almost normal. Both the hyperglycemia and glycosuria vary without relation to the carbohydrate intake. Insulin has practically the same effect on this type as on pancreatic glycosuria.

Clinical Manifestations of Pituitarism Associated with Disorders of Other Ductless Glands.—Hypopituitarism is often added to *congenital hypothyroidism* in juvenile patients. In many such patients between five and ten years of age only one lobe of the hypophysis is involved. The secondary deficiency of the anterior lobe alone produces *thyropituitary insufficiency* which results in *emaciated cretinism*. When deficiency of the posterior lobe, with or without involvement of the anterior lobe, accompanies primary congenital hypothyroidism, there develops the typical girdle adiposity (juvenile adiposity) with the initial signs of hypothyroidism. This syndrome is *obese cretinism*. In young adults hypopituitarism is often complicated by hyperthyroidism. This condition is sometimes mistaken either for myxedema, on account of the sudden and persistent gain in weight, or for an aberrant type of hyperthyroidism, because of the nervous symptoms and the increased basal metabolic rate. The treatment necessary is that required by the primary hypopituitarism; this frequently entirely relieves the hyperthyroidism. In the late post-adult age hypopituitarism —usually bilobar—is often complicated after three or four years by hypothyroidism. This is just the reverse of those changes of early childhood, in which the thyroid gland is first involved. The *pituitary-thyroid* syndromes of late post-adult life are sometimes associated with somnolence or hibernation, and respond very well to pituitary-thyroid treatment. A mild hypothyroidism superposed on bilobar hypopituitarism and later complicated by the menopause often terminates in one of the most severe pluriglandular disorders with symptoms referable to all these glands.

Diagnosis.—The diagnosis of pituitary disorders is ordinarily not difficult when the condition has persisted for more than six months. Not only the gland involved but also the lobe or lobes and the type of abnormal activity must be determined. The age at onset and the etiology (neoplasm, men-

strual epochs, trauma, infection, intoxication, etc.) should be ascertained. The diagnosis of neoplasm depends almost solely on the presence of signs of local and general intracranial pressure. That of aneoplastic pituitarism, either hypo-activity or hyperactivity, is based on the identification and interpretation of the general, regional, and laboratory hormonic signs. The clinical classification is of diagnostic value in determining the prognosis and the type of treatment. Differentiation from hypothyroidism in adults depends on the type of individual, distribution of adiposity, basal metabolic rate, etc.

Simultaneous involvement of the pituitary and thyroid may be recognized by the course and the signs characteristic of each condition. The effect of therapy is a valuable guide in duoglandular involvement of long duration which produces syndromes so mingled as to be almost inseparable. In hypopituitary-hyperthyroid individuals the high basal metabolic rate and the increasing weight and characteristic distribution of adiposity, associated with the typical course of the disease, are sufficient basis for diagnosis. In early thyro-pituitary disorders, in which cretinism is complicated by insufficiency of either the anterior or the posterior lobe of the pituitary, the diagnosis may be made by such early signs of hypothyroidism, as overweight at birth, late dentition, late walking and talking, and mental retardation, to which is added in early childhood either evidence of insufficiency of the anterior lobe or the juvenile obesity of posterior lobe deficiency. The clinical syndromes of adolescent and post-adult life are recognized by the striking dominant manifestations in the pituitary complex.

Prognosis.—The prognosis of pituitary disorders depends on numerous factors. Pituitary tumors are of the most prolonged intracranial type and their rate of growth is contingent on their character. Many tumors of the craniopharyngeal duct become cystic, attain a certain size, and then remain stationary, or even diminish in size, producing symptoms of local pressure which are non-progressive, while there is a remission of the other symptoms of intracranial pressure, such as headache, choking of the disk, photophobia, etc. Malignant hypophyseal neoplasms are progressive and gradually produce more marked local and general intracranial pressure. The prognosis depends on the signs of progress more than on the recognition of pituitary tumor. Serial radiograms of the sella, and perimeter charts, with the general signs of intracranial pressure, should denote the increasing, stationary, or retrogressive character and indicate the possible necessity of surgical treatment.

The prognosis of functional pituitary disorders which produce local or general pathogenic, hormonic signs depends on four factors: the age at which the disorder begins; the duration of the disorder before treatment is instituted; the type of activity of the lobe or lobes producing the disorder; and the number of other glands secondarily involved. Usually, the earlier the onset of the condition, the more definite is the reaction to treatment, provided therapy is begun within a few years after the onset. The shorter the duration before treatment, the more favorable is the prognosis of a simple pituitary disorder. The fewer glands secondarily involved by initial hypopituitarism, the more effective is the suitable treatment. Hypoactivity responds more favorably than hyperactivity.

Treatment.—The treatment employed for pituitary disorders is de-

termined by the etiology and the type of abnormal activity. If the condition is of neoplastic origin, therapeutic measures must be adapted to progressive growth of the tumor or to the stationary or regressive stage. A pituitary tumor which has ceased to grow or has begun to decrease in size cannot be benefited by operation, *x*-rays, or radium. With the exception of gumma of the hypophysis, all progressive tumors should be operated on in the early stages before the surrounding structures, particularly the optic tract and chiasm, have suffered much injury. If *x*-ray treatment is to be used, it should follow rather than precede operation. Patients with progressive pituitary tumors, who refuse to be operated on, may be treated with the high voltage *x*-ray. Radium is not very efficacious because of its lack of penetration. Gummatous tumors of the hypophysis require the same intensive antispecific therapy as does any gumma of the nervous system.

The treatment of all aneoplastic pituitary disorders depends on the activity of the lobe involved. Hyperactivity is combatted with exposure to the high voltage *x*-ray if it produces pathological complexes: and hypoactivity should be treated by administration of the active principle of the lobe or lobes involved. This substance is given both hypodermically and orally at the same time. The preparations used for oral administration are preferably the desiccated substances of the individual lobes of the hypophysis, but the fresh gland, various emulsions, and other preparations are advocated by some authors. The desiccated substance should be administered in doses of gr. v to xv (0.3–1 gm.), and may be obtained under the name of *Anterior Lobe Pituitary Substance*, *Posterior Lobe Pituitary Substance*, or *Entire Gland* (containing glandular substances of both lobes). The simple oral administration has not been found efficacious except in mild adult hypo-activity or in the initial insufficiencies of childhood. No satisfactory enteric capsule has been devised which will prevent gastric digestion of these pituitary preparations. Consequently it is most effective to give extracts of the individual lobes hypodermically. These are known as *Antuitrin*, *Tethelin*, etc. (anterior lobe), and *Pituitrin*, *Pituitary Extract*, *Infundin*, *Liquor Hypophysis*, *Pituitary Liquid*, etc. (posterior lobe). As large a dose of the extract of the anterior lobe as is necessary to relieve the symptoms may be employed without producing untoward results. The author has used as much as 6 c.c. of Antuitrin intravenously without producing any unfavorable reaction. Ordinarily ♏xv to xxx (1–2 c.c.) once a day or less often, according to the severity of symptoms and the reaction to treatment, is adequate. In attempting to relieve the insufficiency of the posterior lobe, care must be exercised in hypodermic administration of the extracts. Three clinical reactions to injection of these posterior lobe preparations permit determination of the physiological dose: the *vascular;* the *intestinal;* and the *general.* The "vascular reaction" is the earliest and occurs a few minutes after hypodermic injection of the preparation of the posterior lobe. It is produced by a comparatively small dose of the extract and consists of an intense pallor, without other symptoms, which lasts for about fifteen minutes. It is undoubtedly due to constriction of the superficial arterioles, which are easily affected by extracts from this lobe of the hypophysis. A larger dose produces the "intestinal reaction" which consists in contraction of the intestinal involuntary muscles and causes abdominal cramps and colic, followed by defecation.

These manifestations are noted within ten to thirty minutes after the hypodermic injection of the extract. This reaction is considered the index of the maximum physiological or tolerable dose, which should not be exceeded if unfavorable results are to be avoided. For ordinary adult insufficiency of the posterior lobe of the pituitary gland, ℥xv (1 c.c.) of pituitrin (0) is given hypodermically. Each dose is increased by ℥i only until the intestinal reaction occurs. This dosage has been found adequate to supplement the lack of normal internal secretion of the posterior lobe in most cases. If it does not relieve the symptoms, the only means of intensifying the medication is to decrease the intervals between the injections until the patient receives one or two doses each day. Should larger amounts be given the "general reaction" would result. This consists in prolonged and intense pallor which sometimes lasts many hours, severe palpitation and tachycardia, syncope, and emotionalism. The general reaction, however, has not been found to precede the intestinal, and can be avoided by not exceeding the dose which produces the intestinal reaction. Ordinarily one or two injections of the amount which elicits the intestinal reaction are given weekly. If this does not control the symptoms and does not reduce the weight and circumference measurements (particularly about the girdle region), relieve the menstrual disturbances, decrease the polyuria and polydipsia, or change the mentality, the interval between doses should be shortened. As many as two or three doses of preparations of the posterior lobe of the pituitary can be given daily, if necessary.

The treatment of pituitary-thyroidism or thyro-pituitarism must vary with each case. In the adult hypopituitarism, in which hyperthyroidism complicates the condition, therapy directed to the hypopituitarism usually relieves both glandular disorders. In the thyro-pituitary syndrome of childhood and in the pituitary-thyroidism of late adult life pituitary and thyroid treatment to the limit of tolerance must be combined. Children two to three years old frequently require gr. ii to v (0.12–0.3 gm.) of desiccated thyroid gland a day. The best index for regulation of the dose at this early age is the rectal temperature. One dose of desiccated thyroid substance should be given daily in milk or with other food. The initial quantity may be gradually increased, by gr. $\frac{1}{4}$ to $\frac{1}{2}$ (0.015–0.03 gm.) each week or ten days, until the rectal temperature is raised to 100.5° F. If all other causes of fever can be excluded, this rise in the rectal temperature to 100.5° F. in infancy may be considered the normal index of a maximum tolerable dose of thyroid. Pituitary substance, anterior or posterior, according to the lobe involved, should be given with thyroid preparations by mouth in these cases. The active principles can be given hypodermically if oral medication does not produce a definite effect.

William Engelbach.

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Diseases of the Suprarenal System

The suprarenal system consists of the suprarenals proper, the accessory suprarenals, the carotid gland, and the paraganglionic bodies. The suprarenals proper lie imbedded in the renal fat and cap the mesial anterior poles of each kidney. The accessory suprarenals are variable in size and number as well as in location. The paraganglionic bodies, so-called because of their relationship to the sympathetic ganglia, undergo retrogressive change after birth, and in the adult can rarely be recognized except on microscopic examination.

The cortex and medulla of the suprarenals are readily distinguishable on gross section; the cortex being yellowish because it contains fat and lipoid; the medulla, reddish brown because of its vascularity. The epithelial cells of the medulla are arranged irregularly in columns and clusters in intimate association with venous sinuses. When treated with chromium they stain dark brown, a reaction which has given to the suprarenal system the name chromaffin system. The degree of reaction to the chrome salts is a direct measure of the secretory activity of the medullary portion of the gland. The cells of the cortex develop embryologically from the Wolffian Ridge in conjunction with the sex glands; the medullary cells are derived from the neural crest with the anlage of the sympathetic nerve cells. Both of these embryonic relations are of the utmost importance in a discussion of the physiology and pathology of the suprarenals.

The Suprarenal Cortex

Physiology and Experimental Pathology.—In man removal of the suprarenal cortex is fatal. The operation does not always cause death in rats

because accessory cortical substance is present. If cortical tissue is grafted into the kidneys before removal of the true suprarenals, the animals survive. When these grafts are later removed the animals show signs of suprarenal exhaustion and die.

Toujan obtained a *pressor substance* from the cortex, similar in all respects to epinephrin, which led him to suggest that epinephrin may be produced in the cortex and stored in the medulla. There are still many adherents to this view. Voegtlin and Macht obtained a different type of pressor substance by extracting suprarenal cortex with chloroform. There is some evidence to show that the suprarenal cortex exerts an *antitoxic* action. Emulsions and extractives of the suprarenal cortex have been found to neutralize tetanus toxin and cobra venom *in vitro*. The fact that the suprarenal cortex undergoes marked degeneration in fatal septicemia and diphtheria, has been interpreted as evidence of its hyperactivity.

The suprarenal cortex enlarges during pregnancy and the nursing period, and also very rapidly in young individuals during the period of growth and development. In many cases of sexual precocity it is hyperplastic, at times to the point of malignancy. In the senile type of nanism the suprarenals have been found to be fibrosed. Feeding of cortical substance to young guinea-pigs causes a very definite increase in the size and weight of the sex glands. The most obvious of the functions of the suprarenal cortex is its fairly distinct influence upon growth and sex differentiation. It is with this latter function only that clinical syndromes have so far been associated. Probably, however, there are other functions of the nature of which we have now no conception.

Clinical Syndromes.—Hirsutism, most frequently recognized in women, is characterized by an abnormally large growth of hair on the face, chest, arms, and legs, and in the midline of the abdomen. The other secondary sex characteristics are maintained, although menstruation is usually irregular. The condition may develop at any period during life and is quite common during or following the menopause. At postmortem examination the suprarenal cortex almost always shows evidences of hyperplasia. There is little hope of remedy. The writer recalls one young girl in whom the condition responded quite markedly to ingestion of small doses of corpus luteum and posterior pituitary extracts, but this type of treatment is not always successful.

Virilism.—In virilism, not only is there a marked increase in the distribution of hair but also a recession of the feminine characteristics. Menstruation ceases, the breasts atrophy, the voice becomes deeper, and at times a beard as heavy as a man's develops. Several cases of this syndrome have been associated with the development of hypernephromata. Our present knowledge renders therapy of little avail.

Precocious Puberty.—Some, but by no means all, cases of precocious puberty are associated with hyperplasia of the suprarenal cortex and usually with the formation of hypernephromata. The condition is most often seen in girls, but is not limited to the female sex. The *female type* is characterized by the onset of menstruation, the development of the adult female contour, increase of body hair, and the development of sex consciousness and libido. The *male type* is manifested by an increase in the size of the genitalia, the onset of spermatogenesis, sex consciousness, and the adult type of muscular development (infant Hercules). Both types are nearly

always associated with malignancy of the suprarenal cortex. The *therapy* is that of the malignant growth. The *prognosis* is the same as in any case of malignancy. Occasionally operative intervention proves successful and renders the sexual state of the child normal.

WALTER TIMME.

THE SUPRARENAL MEDULLA

Physiology and Experimental Pathology.—To Takamine belongs the credit of first isolating the active principal of the suprarenal medulla (adrenalin) by a commercially practical method. Later methods were devised for preparing this substance synthetically, among the most notable of which is that of Stolz.

The action of epinephrin (adrenalin) is parallel to that of sympathetic stimulation; and it has been fairly well determined that the substance acts only on tissues with a sympathetic nerve supply. It is not discharged into the blood-stream except when these tissues are sympathetically stimulated. While accessory chromaffin tissue (carotid and paraganglionic bodies) is known to contain epinephrin, its sympathetic nerve supply has never been discovered and its influence as an incretory organ is probably negligible. Epinephrin is thought to act on a hypothetical tissue—the receptor substance—which mediates between the neural junction and the cell. This is assumed because epinephrin is active after section and subsequent degeneration of the sympathetic fibers, including the neural junction. When the sympathetic supply is paralyzed with apocodein, however, there is no epinephrin action, although the cell still responds to a direct stimulant such as barium chlorid. Since in small amounts epinephrin relaxes smooth muscle and in larger amounts causes contraction, it exercises both depressor and pressor effects on the circulation. There is considerable evidence that it increases the quantity of sugar in the blood, a fact which is very important in the physiology of muscular exertion and heat regulation. That this action is independent of the thyroid has been demonstrated by Cannon.

Clinical Syndromes.—The syndromes clinically associated with the suprarenal medulla result from medullary deficiency. Hypersecretion doubtless occurs but its symptomatology is so complex and so easily confounded with other conditions that it is not recognized. For example the tremor, palpitation, anxiety, mydriasis, choking sensation, and some of the gastrointestinal symptoms attributed to hyperthyroidism might reasonably be produced by hyperadrenalism or by irritative lesions in the region of the large sympathetic ganglia. Differential diagnosis is extremely difficult. These conditions are called sympathetic instability or irritability, and comprise a part of the syndrome of many conditions varying from mild intoxication to so-called psychoneurosis.

ACUTE SUPRARENAL INSUFFICIENCY.—*Etiology.*—Any severe mental, physical, infectious, traumatic, or toxic strain upon an already inadequate suprarenal system initiates acute suprarenal insufficiency.

Morbid Anatomy.—Vacuolization and fragmentation of the chromaffin

cells has been seen in such cases. The lesion is not confined to the suprarenal bodies alone, but involves the sympathetic nervous system and occasionally the central nervous system.

Symptoms.—The symptoms are those of shock—extreme prostration, running pulse, rapid, shallow respirations, low blood-pressure, low blood-sugar, and subnormal temperature. If no relief is afforded, prostration soon gives way to coma and death.

Prognosis.—Unless definite improvement promptly follows treatment, the prognosis is poor.

Treatment.—Symptomatic and supportive treatment is necessary. The body must be kept warm and adequate stimulation, in the form of caffein or strychnin, administered. Enemas of hot coffee are quite effective. Adrenalin is not so dependable a form of medication as caffein and strychnin. It should never be given in doses of more than 10 minims; and if immediate improvement is not noted the dose should *not* be repeated.

WALTER TIMME.

CHRONIC SUPRARENAL INSUFFICIENCY (ADDISON'S DISEASE)

Definition.—Chronic suprarenal insufficiency was first described by Addison in 1855. "The disease develops in the third and fourth decade of life, usually insidiously, with adynamia and apathy To these are added disturbances of the digestive tract (constipation alternating with diarrheas), pigmenting of the skin and mucous membranes: the patients succumb under a gradually increasing cachexia, not rarely with stormy terminal manifestations; autopsy most always shows disease of both suprarenals, mostly tuberculous caseation."

Etiology.—This disease is rare. Osler observed but 17 cases in the United States. Males are more often affected than females. In between 80 and 90 per cent. of cases which come to autopsy, some destructive lesion of the suprarenals can be demonstrated. Tuberculosis is the most common cause, simple atrophy next. Infection, intoxication, trauma, and new growth are all possible etiological factors.

Morbid Anatomy.—Rolleston summarizes the various conditions found in the suprarenal bodies as follows:

"1. The fibro-caseous lesion due to tuberculosis—far the commonest condition found. 2. Simple atrophy. 3. Chronic interstitial inflammation leading to atrophy. 4. Malignant disease invading the capsules, including Addison's case of malignant nodule compressing the suprarenal vein. 5. Blood extravasated into the suprarenal bodies. 6. No lesion of the suprarenal bodies themselves, but pressure or inflammation involving the semilunar ganglia.

"The first is the only common cause of Addison's disease. The others, with the exception of simple atrophy, may be considered very rare."

Symptoms.—The characteristic onset is gradual and insidious.

Asthenia is frequently the first symptom observed. The patient complains of fatigue and is unable to perform his accustomed tasks without great effort. The blood-pressure is low and gradually decreases as asthenia

becomes more marked; the systolic pressure in the profound states sinks as low as 60 or 70 mm. of Hg. The pulse is soft and weak. The hands and feet are cold, and patients feel cold subjectively. Often the temperature is subnormal—especially in the later stages. There is a diminution and eventual loss of libido and sexual power, and menstrual irregularities and subsequent amenorrhea.

The blood-sugar is low—occasionally so low as to cause convulsions. Dizziness, headache, backache, and vertigo are frequent symptoms.

The asthenia is gradually progressive, and prostration is complete in the latter stages of the disease.

Simultaneously with the weakness and fatigability *nervous symptoms* appear. The depression, listlessness, and apathy vary in degree; there is mental and physical retardation, and lack of initiative. The apathy may be interrupted by periods of irritability, apprehension, and excitement which at times amounts to delirium. Occasionally this is a terminal stage.

Characteristically the face becomes darkened by patchy *pigmentation.* The hands, neck, mucous membranes, and trunk may also be involved, in the order named. The discoloration of the trunk is located along the lines of cleavage of the skin or where there is friction from the clothing. Often pigmentation is the outstanding early symptom of the disease. The pigment is probably melanin.

The general asthenia affects the smooth muscle of the *gastro-intestinal tract* and causes loss of tone with its consequent symptoms—gas, distention, fulness after eating, putrefaction, toxic absorption, and constipation with occasional diarrhea.

Anemia is not a characteristic of this disease. The sallow complexion is due not to lack of blood but to poor peripheral circulation. The *urine* shows no characteristic abnormality. The *basal metabolism* is low.

The disease is progressive and death may follow intercurrent infection, syncope, or gradually increasing cachexia and exhaustion.

Diagnosis.—In the early stages, diagnosis is difficult. Pigmentation, associated with the marked, persistent, and progressive asthenia, should permit diagnosis, but pigmentation may occur in many other conditions. Because of the frequent association of this disease with tuberculosis, Osler suggests the use of the tuberculin test. He considers a positive test in the early stages as very suggestive of Addison's disease.

Prognosis.—The efficacy of treatment is of course doubtful, for if the early symptoms disappear the disturbance may not have been true Addison's disease. Occasionally, a well-developed case improves for a while, but ordinarily the disease is slowly progressive and terminates with death.

Treatment should be instituted early. Aside from the general hygienic measures of administration of wholesome, easily digested food, regular hours, plenty of rest, fresh air, sunshine, and regulation of the intestinal tract, supportive treatment for the asthenia is desirable. Suprarenal substance (dried gland) may be given in doses of 1 grain twice daily after meals; or small doses of thyroid (0.1–1 gr. daily) and sodium iodid (5 gr. daily). These may be supplemented with small doses of pituitary (dried gland, $\frac{1}{4}$–$\frac{1}{2}$ gr. daily). All of these substances tend to increase the quantity of sugar in the blood and combat the asthenia. Strychnin and arsenic, preferably given hypodermically, are also of value. These two substances are conveniently prepared together in ampoules in the form of cacodylate

of soda and strychnin. The contents of one ampoule (soda, gr. $\frac{3}{4}$; strychnin, gr. $\frac{1}{60}$) should be administered hypodermically every other day or every day as the case may require. In advanced cases, when the asthenia is severe, the dosage of strychnin may be increased to gr. $\frac{1}{30}$, or even gr. $\frac{1}{15}$, once or twice daily.

WALTER TIMME.

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DISEASES OF THE THYMUS GLAND

THE thymus is a gland derived embryologically from the third and fourth branchial clefts. In relation to the body weight it is largest at the time of birth, but it attains its greatest weight at puberty. Thereafter it diminishes in size with varying degrees of rapidity in different individuals. Although there is little or no experimental basis for the assumption that the thymus is an incretory gland, clinicians persist in associating several very interesting syndromes with irregularities in its activity. These are well worth careful consideration.

Pathology.—Like any other portion of the human economy the thymus gland is subject to pathological change. Throughout the course of any generalized disease process the thymus falls heir to its share of disturbance and we get active and passive congestion, edema, acute and chronic inflammation, and resultant atrophy and fibrosis; but as these conditions are met with only as part of a generalized morbid process the thymic symptoms deserve no special mention here.

Tumors.—*Benign tumors* of the thymus are rare. Lipomata, fibromata, dermoid cysts, ciliated cysts, and congenital syphilitic cysts (so-called DuBois abscesses) have all been described at one time or another in the literature. To recognize them during life, however, would indeed be an accomplishment. True thymic hyperplasia will be discussed later.

The *primary malignant thymomata* include carcinoma and sarcoma, of which lymphosarcoma occurs most frequently. The symptoms of both are practically identical, and are those of pressure in the upper mediastinum, including stridulous breathing, dysphagia (esophageal pressure), and cardiac irregularity due to direct pressure and sympathetic and vagus disturbances. The signs are enlargement of the superficial veins over the upper chest, frequently a peculiar cyanosis of the hands, increased mediastinal dulness, and the presence of a large shadow in the region of the thymus on *x*-ray examination.

Treatment consists in prompt irradiation with massive doses of *x*-ray or radium. These tumors are almost invariably fatal in spite of prompt and vigorous treatment.

Status Thymicolymphaticus and Timme's Multiglandular Syndrome are of necessity described together because the one is a natural sequence of the other. A certain number of individuals are born with a definite inherited type of diathesis which is known as *status thymicolymphaticus*. At birth such individuals have enlarged thymic glands and a tendency to general lymphoid hyperplasia. As a rule their skin is extremely fine and smooth and they have beautiful pink complexions. They are subject to attacks of cyanosis, which at times is so severe that it causes unconsciousness, convulsions, and not infrequently sudden death (Mors Thymica). Sometimes death occurs without any warning or preceding cyanosis; an apparently healthy child may be found dead in its crib. Autopsy then reveals enlargement of the thymus.

When the thymus is particularly large, individuals are subject to attacks of *thymic asthma, i. e.*, symptoms of pressure in the upper mediastinum. Prompt treatment with *x*-ray and, in some cases, thymectomy are said to cure this condition. In all probability such symptoms are produced by true thymic hyperplasia which progresses so slowly that the organs of the chest can accommodate themselves in some measure to the pressure changes.

Until recently *status thymicolymphaticus* was recognized chiefly at postmortem and this condition had become associated in the mind of the practitioner with swift and unexpected death. As a result of our efforts to recognize this condition during life it is now established that most of these patients do not die. That they do not die is because certain changes take place in the bodies of these individuals, a study of which led the author to postulate his thymus-suprarenal-pituitary syndrome.

"*Status hypoplasticus*" is a better name for the condition, for it describes the marked lack of differentiation during development. The children mature very slowly, and secondary sex characteristics are late in appearing. The epiphyses remain ununited, and growth is disproportionate, the arms and legs being too long for the trunk. The developmental abnormalities range from almost complete infantilism to the presence of a maxillary torus in an otherwise structurally perfect individual. Failure of differentiation is not confined to the structure, but includes physiology, chemistry, and mental and behavioristic fields as well. Physiologically patients tend to the *habitus asthenicus* type, with low blood-pressure, flabby musculature, and lack of resistance to fatigue and infection. Chemically they are predisposed to low blood-sugar, acidosis, and prolonged coagulation time of the blood. There is usually a relative lymphocytosis. In respect to behavior they remain children. They follow the path of least resistance, shirk responsibility, and lack the ability to concentrate. Consequently, they are apt to feel inadequate and inferior.

Diagnosis.—The combination of a structural abnormality and any one of the physiological, chemical, behavioristic, or mental tendencies mentioned, with or without definite *x*-ray evidence of an enlarged or persistent thymus gland, serves to establish the diagnosis of status thymicolymphaticus.

Treatment of this condition must be based upon a knowledge of the mechanism by which the body automatically attempts to overcome the

hypoplastic tendency. This is best obtained by outlining the author's theory. He believes that to overcome the effect of the characteristically small blood-vessels, low blood-pressure, low blood-sugar, and consequent asthenia, increased demands are put upon the suprarenals. The thymic mass itself by pressing on the vagus and sympathetic plexuses about the base of the heart and great vessels causes a maladjustment of the automatic regulatory control which enables the body to meet emergencies. Slight excess pressure on the vagus may stop the heart. The suprarenal system, which is continually pushed to the limit, cannot meet the emergency. The heart stops beating. There is no rebound. The patient dies. Other forms of death are produced by hemorrhages into the ventricles of the brain, and into the suprarenal glands. The individual who lives has the larger and more competent suprarenal system, which, in perfectly compensated individuals, enlarges sufficiently to more than meet the added demands upon it. Later on this system hastens maturation of the sex glands, the development of secondary sex characteristics, and the attainment of physical and mental poise.

The pituitary gland is also part of the compensatory mechanism. A fully adequate secretion from this gland can overcome the hypoplastic structural tendencies of the thymic state, raise the blood-sugar, increase resistance to fatigue, and, in all probability, further development of the central nervous system, and thus aid in overcoming childish behavioristic and mental tendencies.

The following therapy is based upon the facts just outlined. Enlargement of the thymus in an infant should be treated by exposure to *x*-ray and administration of small amounts of sodium iodid (gr. 1–3, daily). Other individuals profit most from pituitary medication. Although medication is, of course, most necessary when the body fails to overcome deficiencies, *i. e.*, when symptoms appear, future difficulties may be avoided, if the tendency to status thymicolymphaticus is recognized early and treatment instituted at the proper time. Pituitary (both whole gland and anterior lobe) should be administered to the limit of tolerance by mouth and hypodermically. Suprarenal gland and adrenalin are of great value in relieving the extreme fatigue. Pituitary is more efficacious if combined with small amounts of sodium iodid (gr. 2–5, daily) and occasionally with small doses of thyroid (gr. $\frac{1}{10}$–$\frac{1}{2}$ daily).

The Thymus in Myasthenia Gravis.—The not infrequent association of thymomata with myasthenia gravis has led certain writers to believe that there is a close relation between this condition and thymic abnormality. In 1901, Weigert described 2 cases of thymic tumor in myasthenia gravis; and many others have since been reported. Pathological examination of the affected muscles reveals lymphorrhages which further emphasize the relation of this condition to the thymic tumor.

All patients with myasthenia gravis should be carefully examined for evidences of an enlarged thymus. If these are found vigorous treatment with *x*-ray should be given.

Walter Timme.

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Diseases of the Parathyroid Glands

The parathyroid glands are usually found in pairs on the posterior surface of the lateral lobes of the thyroid. Most frequently only two pairs occur, the superior and inferior, although as many as four are sometimes present. At times there is an extra gland on one side. Their blood-supply is derived from the inferior thyroid artery. Sympathetic nerve endings are present in the gland cells.

Vassale and Generali (1900) were the first to suggest a relation between parathyroid extirpation and the symptoms of tetany which in certain species of animals followed the removal of these bodies. The fact that tetany develops in certain animals and not in others has not yet been explained. A large amount of experimental work on the parathyroids has brought to light the following facts: (1) parathyroidectomy in animals and man usually causes symptoms of tetany; (2) transplantation of parathyroids and injection of parathyroid substance ameliorates and sometimes cures such tetany; (3) in tetany there is a disturbance of the acid-base equilibrium, a decrease of the sedative ions (calcium and magnesium) in the blood and body tissues, an increase of the irritating ions (potassium and sodium), and an increase of guanidin and its derivatives, which have been shown experimentally to cause a condition closely resembling tetany; (4) youth, sedentary occupation, a shut-in environment, and unbalanced food predispose to the development of tetany; and (5) sustained voluntary or involuntary hyperpnea initiates symptoms of tetany in an otherwise normal individual.

The fact that there is a lowering of the calcium content of the tissues in tetany and that injections of calcium give rise to an improvement or disappearance of the symptoms led MacCallum to believe that a disturbance of calcium metabolism is the underlying cause of this condition. But since injections of strontium, barium, and magnesium produce like results, and bleeding and hypodermoclysis likewise cause improvement, most observers conclude that the *function of the parathyroids is detoxification*, and that when the parathyroids are removed or are rendered inefficient toxic substances such as guanidin accumulate in the tissues and produce a nervous excitability and the syndrome of tetany.

Collip (1925) has obtained an extract from the parathyroid gland which relieves tetany, increases the blood calcium, and prolongs life in parathyroidectomized dogs. Excessive or prolonged administration of this extract produces a very high calcium and phosphorous content in the blood-serum and is accompanied by convulsions and death. Greenwald and Gross have studied the effect of thyroparathyroidectomy on the excretion of calcium, phosphorus, magnesium, and nitrogen, and also the changes produced in the excretion of these substances by administration of calcium salts, sodium phosphate, and potent parathyroid extract. Parathyroid extract raises the blood calcium apparently by mobilizing it from the bone.

TETANY

Definition.—Tetany is an affection characterized by a peculiar hyperexcitability of the nervous system (motor, sensory, and autonomic) which,

when marked, causes tonic spasm of the muscles. These may be chronic or intermittent, generalized or local.

Etiology and Occurrence.—The condition is thought to result from a disturbance of parathyroid function.

According to Frankl-Hochwart there are several types:

Tetany of Adults.—(*a*) *Epidemic tetany* (rheumatic tetany, idiopathic workman's tetany, or shoemaker's cramp), which in certain parts of Europe prevails widely, particularly in March and April. Von Jacksch has described an epidemic form which occurs in young men of the working classes. It is sometimes accompanied with slight fever, and in the opinion of von Jacksch is infectious. This form is acute, lasts only two or three weeks, and rarely proves fatal.

(*b*) *Tetany of gastric and intestinal disorders* (dyspepsia, gastrectasis, diarrhea, and helminthiasis). This is rarely associated with dilatation of the stomach. Not more than 30 cases have been reported.

(*c*) *Tetany of the acute infectious diseases* (typhoid, cholera, influenza, measles, scarlatina, etc.).

(*d*) *Tetany following poisoning* from chloroform, morphin, ergot, lead, alcohol, and uremia occurs only in isolated cases.

(*e*) Tetany may also develop during *pregnancy* and recur in successive pregnancies. Because it appears in nursing women, Trousseau calls it "*Nurse's contracture.*"

(*f*) The tetany which follows *removal of the thyroid gland* is probably due to simultaneous removal of the parathyroid bodies.

(*g*) Tetany may complicate other *nervous disorders*, such as Basedow's disease, cerebral tumor, cysts of the cerebellum, and syringomyelia.

Tetany in Children.—Tetany bears a definite relation to gastrointestinal disorders, acute infections, and rickets in childhood. Mild cases are not uncommon, particularly in connection with rickets and gastrointestinal disturbances. Probably tetany and spasmophilia are but different degrees of the same phenomenon.

Morbid Anatomy.—Various pathological changes—hemorrhage, scars, cysts, atrophy, round-cell infiltration, and ruptured lymph-spaces—have been said to occur in the parathyroids of patients with tetany. Winternitz demonstrated miliary tubercles in the parathyroid glands of a patient with pulmonary tuberculosis complicated by tetany. Pathological changes, however, have also been described in the parathyroids of individuals with no symptoms of tetany.

MacCallum states that signs of acute degeneration of the anterior horn cells of the spinal cord and of the cells of the cerebral cortex occurred in his animals with experimental tetany.

Symptoms.—The symptoms may be latent (induced by certain stimuli) or manifest (occurring spontaneously). They usually appear abruptly and consist of intermittent tonic contractions of certain groups of muscles, frequently those supplied by a certain nerve (brachial, lumbosacral). This results in the assumption of characteristic attitudes, such as the obstetrical hand and carpopedal spasm. These are by no means always the same, for the position assumed depends on the nerves involved. The spasm is most frequently bilateral but at times only one arm or leg, or one side of the body is affected. It at times involves the muscles of the larynx (laryngismus), face, jaw, neck, trunk, eye, and diaphragm. Frequently the spasm shifts

from one part of the body to another, or it may occur in many parts simultaneously. The duration of each spasm, of the intermissions, and of the entire attack is quite variable. In severe cases the spasm may be continuous and persist until medication or surgical intervention brings relief. In others the attack ends spontaneously within a few hours. The smooth muscle of the bronchi, vascular system, digestive apparatus, and urogenital tract may also be affected. There is no loss of consciousness.

Hyperesthesia of the sensory nerves may be present, and pain and paresthesia in the affected parts occur frequently. Electrical and mechanical stimulation of sensory nerves elicits increased response which frequently initiates a tetanic spasm (Hoffman's sign). Attacks of tetany may be followed by flaccid or spastic paresis of the extremities and rarely by a definite psychosis. Occasionally the tetany is accompanied by epileptiform seizures.

Signs of Tetany.—Certain phenomena or signs more or less pathognomonic of tetany deserve mention. They are usually associated with the name of the man who first described them.

Erb's Sign.—There is an increased electrical excitability of the motor nerves in tetany, which has been determined with great nicety and, alone, is sufficient basis for the diagnosis of tetany. The occurrence of a cathodal opening contraction (COC) with a current of less than 5 milliamperes serves to make the diagnosis. The anodal opening contraction (AOC) is greater than or equal to the anodal closing contraction (ACC) in this condition.

Trousseau's Sign.—If a ligature about the upper arm is sufficiently tight to suppress the flow of blood through the brachial artery, a typical tetanic spasm of the hand and forearm develops in patients with tetany. In extreme cases this phenomenon may be elicited simply by exerting pressure with the finger over the bicipital groove.

Chvostek's sign is based upon hyperexcitability of the facial nerve, which, although it does not occur in all cases of tetany, is fairly characteristic when observed. If the region of the *pes anserinum* in front of the ear is tapped with the finger or a percussion hammer, a spasm of the facial muscles of that side of the face results when the sign is positive. In mild cases only a slight twitching of the angle of the mouth or about the eye results, but in severer forms, a definite spasm of the entire side of the face may be elicited.

Pool's sign is often spoken of as the *arm and leg phenomenon*. The mechanical stimulus used to produce the spasm is tension applied to the brachial plexus or the sciatic. Forcible abduction of the arm in tetany often causes spasm of the muscles of the hand and arm, and, likewise, forcible flexion of the thigh on the trunk with the leg extended (Lasseque's position) produces spasm of the muscles of the foot and leg.

Hoffman's sign depends on the production of a muscular spasm by mechanical or electrical stimulation of a sensory nerve.

Diagnosis.—Tetany is easily recognized. It may be confounded with the various *functional tics* and *habit spasms*, *dystonia musculorum*, *dystonia from organic brain disease*, and *myotonia*. The presence of any of the above phenomena and the absence of neurological signs determines the diagnosis. Erb's phenomenon is perhaps the most constant and dependable sign.

Prognosis.—In childhood the milder forms of tetany known as spasmophilia offer a good prognosis. The well-defined, generalized form is

more serious. Barker says the mortality is 20 per cent. in such cases. Tetany following parathyroidectomy may prove fatal, but only in a small proportion of cases, as it usually responds to treatment. Idiopathic workman's tetany is almost never fatal: the attacks are liable to recur, but as a rule are progressively less severe. The tetany associated with gastro-intestinal disturbances is fatal in about 70 per cent. of the cases treated medically: when surgical relief of the gastro-intestinal condition is effected only about 30 per cent. of patients die. The tetany of pregnancy is seldom fatal.

Treatment of this condition consists of the following measures: increase of elimination by forcing fluids, diaphoresis, catharsis, and colon irrigations; administration of a low protein diet rich in vitamins; and of calcium in the form of calcium lactate (gr. 5 to 10, by mouth, three times a day) or calcium chlorid (gr. 10 to 20 in water, intravenously, once a day). Parathyroid deficiency may be counteracted by giving preparations of the parathyroid gland by mouth (gr. $\frac{1}{10}$-$\frac{1}{20}$ dried gland, three times a day); more recently, hypodermic injections of parathyroid gland extract have been used successfully in cases of tetany with low blood calcium. Its use is still in the experimental stage, however, and should be carefully controlled by frequent blood calcium determinations. Parathyroid transplantation yields excellent results for a while. The transplants rarely function for any length of time and must be either autogenous or isogenous to be of value.

Exposure to the ultraviolet ray (direct sunlight or rays from quartz lamp) is also helpful, especially in conjunction with calcium therapy. The reason for this is not yet clear, but in some way the ultraviolet ray aids utilization of calcium by the body.

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DISEASES OF THE PINEAL GLAND

The pineal gland is a small cone-shaped body, about 6 mm. in length, which lies on the roof of the mid-brain in the depression between the superior colliculi. Its physiology is still unknown in spite of the fact that the occurrence of sexual precocity in children with pineal tumor has stimulated

much research. Experiments in which various preparations of the gland have been fed to animals seem to demonstrate that hyperactivity of the pineal is the cause of sexual precocity; while observations made after extirpation of this body suggest that such changes result from hypofunction of the pineal gland. These contradictory results indicate that the problem is still unsolved.

Tumors of the Pineal.—The work of the Pellizzi clinic is largely responsible for the clinical association of *pineal tumor* and *macrogenitosomia precox* in children. Boehm, in 1917, found in the literature reports of 12 cases of pineal tumor, associated with early sexual development. Of these 7 were teratomata, 2 alveolosarcomata, 1 glioma, 1 psammosarcoma, and 1 angioblastoma. This seeems to nullify Krabbe's contention that only teratomata of the pineal are associated with sexual precocity. Even teratomata may occur, however, in children without any evidence of sexual precocity. Pineal tumor in the adult is usually associated with *diminution of sexual power* and *libido.*

Symptoms.—The symptoms of pineal tumor are those of brain tumor with or without certain localizing neurological signs, caused by pressure on adjacent structures. Involvement of the corpora quadrigemina usually produces certain pupillary changes: one pupil may be larger than the other, a condition which may be reversed within a few hours; occasionally both pupils are fixed in dilatation. When the nuclei of the fourth nerve, which lie in close relation to the pineal, are involved, the characteristic "skew deviation" of the eyes appears. Any of the cranial nerves may be affected by the remote effects of pressure. This type of tumor frequently causes cerebellar disturbances and occasionally, when there is pressure downward on the cerebral peduncles, pyramidal tract signs. The aqueduct of Sylvius is nearly always occluded and consequently there is a tremendous increase of pressure in the ventricles, marked choking of the disks, and severe headache, nausea, and vomiting.

At times in children—only of the male sex—the following other symptoms develop: (1) over-rapid growth which makes them large for their age, but usually well proportioned; (2) mental precocity so that the intelligence quotient is at times as high as 140; (3) abnormal sexual development which is evidenced by enlargement of the penis and testicles, the appearance of hair on the pubis and in the axilla, changing of the voice, and, at times, by gonadal function (erections, emissions, and masturbation); and (4) in some individuals, symptoms which are most frequently associated with the hypopituitary states, namely, adiposity, polyuria, polydipsia, and drowsiness. These occur usually when the cerebrospinal fluid backs up into the ventricles and there is evidence of increased pressure in the sella turcica.

Diagnosis.—Pineal tumors are rarely recognized during life. In children, the combination of symptoms of brain tumor with bodily overgrowth, and sexual and mental precocity, should always suggest the presence of a pineal tumor.

Prognosis.—The outcome is almost invariably fatal. In the experience of the writer, no cases have ever been arrested or cured.

Treatment.—The corpus callosum should always be punctured to lower the increased intracranial pressure, and thereby to relieve the agonizing headache and save the eyesight. Removal of the tumor is almost out of the question. *x*-Ray therapy is advisable.

Pineal Myopathy.—In 1916, the author described certain types of muscular dystrophy as probably a form of endocrine disease. The syndrome is characterized by (1) progressive muscular weakness with or without atrophy; (2) mental precocity; and (3) the presence of a pineal shadow in x-ray pictures of the skull. So far he has seen 4 cases of this type (classified as progressive muscular dystrophies) which have apparently been cured by ingestion of pineal substance (dried gland, gr. $\frac{1}{5}$, three times a day), and other glandular medication. In several other instances the progress of the disease has been arrested and has remained stationary for several years as the result of treatment, but by far the greater number of patients (34) have continued to fail, although perhaps more slowly.

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DISEASES OF THE SEX GLANDS

DISEASES OF THE MALE GONADS

The testes are now generally believed to produce, in addition to sperm, an internal secretion. The effect of castration in mammalian animals and man is perhaps the most striking experimental evidence of this. Steinach and Sand successfully grafted the ovaries of guinea-pigs into previously castrated males, thus producing "feminized males" who developed characters peculiar to the female. Likewise they reversed the process and produced "masculinized females." Such experiments have demonstrated that the old theory of a nervous control mechanism is not well founded and that the gonads affect the development of somatic sex characteristics by their endocrin secretion. The cells which fill the interstices between the seminiferous tubules and which were first described by Leydig (interstitial cells of Leydig) have been singled out as the elaborators of this incretory element. Embryologically, they are different from the spermatogenic cells. They show periodic activity synchronous with the rutting season in animals. Experimentally, the germ cells have been found to atrophy following exposure to x-ray and also after vasectomy, while the interstitial cells remain intact.

DISEASES OF HYPERSECRETION

Precocious Puberty (*Pubertas precox, Macrogenitosomia precox.*)—In precocious puberty the secondary sex characteristics appear before the

usual age. The condition may develop at any time from birth to the age of twelve or thirteen years. There is an increase in the size of the penis and testicles, and evidence of function such as erection, pollution, and frequently masturbation. Hair appears on the pubis, in the axilla, and on the face; muscular development tends to be of the adult type, and growth is usually retarded. Children in this condition are difficult to control and are fond of embracing children of the opposite sex. There is often a tendency to exhibitionism.

Pubertas precox must be differentiated from *virilismus* and *hirsutismus*. In the former the hair is distributed as in the adult and in the latter there is a general bodily hypertrichosis. In neither is there evidence of gonadal function.

While pubertas precox is undoubtedly an endocrine disturbance in which changes in the gonadal secretion predominate, the primary lesion is often located in other glands. The pineal, pituitary, suprarenal cortex, and testes have each been thought to be responsible for the development of this condition, and consequently the disease may be considered to be of several types.

The Pineal Type.—Most cases of the pineal type are associated with tumors of the pineal body. Intracranial lesions caused by the expanding tumor add complications. Therapy is of little or no avail. In spite of conflicting experimental evidence that the sexual precocity is due to an over-secretion and under-secretion of the pineal gland, oral administration of preparations of this gland (pineal substance, gr. $\frac{1}{5}$, twice daily, after meals) has been found helpful in certain cases not associated with tumor, when the presence of a pineal shadow in *x*-ray plates and muscular asthenia pointed to epiphyseal deficiency.

The Pituitary Type is rare. As it is reported to occur only in the female it will be discussed in the chapter on the female gonads.

The Suprarenal Cortex Type.—The embryological development of both testes and suprarenal cortex from the Wolffian ridge seems to suggest a close relation between these two glands. Experimentally gonadal hypertrophy has been produced in white rats by feeding suprarenal cortex; and additional evidence of their connection is to be found in the fact that numerous cases of pubertas precox are associated with hypernephroma. These tumor cases are usually diagnosed by palpation of a tumor mass in the region of the kidney. *x-Ray* or *radium therapy* affords the only hope of relief because patients cannot withstand the shock of an operation. At best the *prognosis* is poor.

The Gonadal Type.—The well-known case reported by Sacchi is a good illustration of gonadal pubertas precox. A boy at the age of nine, weighed 97 pounds, had secondary sex hair, a deep voice, well-developed genitalia, and frequent erections and seminal emissions. After the removal of an alveolar carcinoma of the left testicle his voice became childlike, the erections and seminal emissions ceased, and the quantity of secondary sex hair gradually diminished.

The Thymus.—It is well known that the thymus shows signs of involution at the age of puberty, and that sexual maturity has been hastened in young animals by removal of the thymus. Hewer finds that administration of thymus gland to young male white rats delays testicular development. Clinically, thymus feeding has been found efficacious in delaying

puberty, but as yet there is not sufficient pathological evidence to justify the designation of a thymic type of precocious puberty.

Treatment is necessary not only to arrest the sexual precocity but likewise to obviate such associated symptoms as stunting, muscular asthenia, and behavioristic abnormalities. Many glandular combinations have been administered, but in the experience of the author the feeding of a mixture of thymus and pineal gland has proved most satisfactory (thymus, gr. 5, twice daily after meals; pineal, gr. $\frac{1}{5}$, twice daily, after meals). Certainly it is the most rational combination.

Hypersecretion in the Adult.—Excessive gonadal activity in the male after puberty is a common condition which is usually seen by the physician only because of inadequate marital relations.

The *causes* of such hypergonadal activity are numerous. Good food, regular hours, plenty of sleep coupled with an active outdoor life and infrequency of sexual intercourse increase the sexual activity of every normal male. Soldiers, sailors, lumberjacks, prospectors, and cowboys furnish examples of this hyperactivity which is usually combined with a libidinous psychical trend. This condition is by no means confined to the great outdoors, however, and is not uncommon in the large industrial centers. Lack of association with the opposite sex and lack of gratification do, however, favor excessive testicular activity and *vice versa*.

Increased activity of the *anterior lobe of the pituitary*, of the *suprarenal cortex*, and of the *interstitial cells of the testes* is likewise a cause of this condition even in individuals not living an invigorating life. Increased sympathetic activity produces the same condition.

The *diagnosis* of excessive gonadal function rests mainly upon the frequency of erections and emissions: the effective factor or libido is not dependable evidence as it is frequently of purely psychic origin, and the sexual appetite so aroused is far greater than the actual sexual power of the individual.

Treatment.—Therapy includes psychotherapy, physiotherapy, and medication. *Psycho-analysis* may be of value in some cases. Intensive occupation, exhaustive exercise, and hot baths on retiring are excellent physical measures. Administration of *glandular products* has been found of little value. The *coal-tar derivatives*, particularly acetanilid, the bromids, and luminal, are the most useful drugs.

Satyriasis.—Markedly increased libido without increased sexual power is not rare. The condition is occasionally found in cryptorchidism, at the male menopause, following the impotence caused by undue exposure to *x*-rays and radium, and in the initial stages of organic testicular disease. This abnormality is most likely to develop in individuals of unstable nervous and mental equilibrium, but an excessive incretory activity in an individual with an unstable psyche or a libidinous trend would undoubtedly produce the same result by over-stimulating an otherwise normal interstitial secretion.

The *treatment* is of the same nature as that outlined above.

DISEASES OF HYPOSECRETION

Anatomical Anomalies.—Hermaphroditism and Pseudohermaphroditism.—As far as is known, true hermaphroditism has never been described in man. Since *diagnosis* of the false sexual types depends upon the character of the sex glands, which are nearly always concealed, regardless of the type

of external genitalia, it is usually possible only after death or by means of biopsy. *Treatment* is of the same nature as for cryptorchidism, but is usually unsatisfactory.

Cryptorchidism may be caused by various anatomical abnormalities such as defects of the mesorchium, paralysis, absence or faulty insertion of the gubernaculum, narrowness of the vaginal process, or large size of the testicle, shortness of the spermatic cord, rudimentary or obliterated scrotum, premature obliteration of the inguinal canal, or adhesions within the abdomen of the inguinal canal following inflammation or trauma. The testes may be held within the abdominal cavity, at the internal ring, or within the canal (inguinal extopia—the common variety). Migration may be aberrant so that the testicle is found in the small pelvis or in a deep crural, superficial crural, cruro-scrotal, pubo-penile, penile, subcutaneous abdominal, or perineal position. A patent vaginal process may permit intermittent migration.

One or both testicles may be involved. *Unilateral cryptorchidism* is the most common type. It occurs frequently in children, but is nearly always relieved with the advent of puberty or shortly afterward. Descent of the testicles may occur, however, as late as the fifty-eighth year. Unless the anatomy absolutely prevents descent, this process may often be hastened by feeding pituitary and thyroid substance in doses up to the limit of tolerance for several months. Results are often obtained within one to two weeks. Bitemporal headaches are a sign of overdosage with pituitary: occipital headaches, palpitation, and increased irritability, of over-ingestion of thyroid.

Before puberty these patients have small genitalia and a tendency to a scrotal fold around the base of the penis. At the usual age of puberty they fail to mature and usually grow very rapidly in height. The beard and secondary hair appear slowly and are sparse and usually reversive in type. The adult characteristics of these individuals are eunuchoid. Aspermatogenesis is the rule; exceptions are rare. Libido is usually lacking or diminished, but may be present or even increased for a while.

Treatment should be started early, preferably just after five years of age, in order to prevent, if possible, the development of a eunuchoid condition. It should continue, however, even if eunuchoidism develops, because it is occasionally beneficial even at the age of thirty or forty. The percentage of failures in older patients is much higher than that of the successes, and *prognosis* should not therefore be too hopeful.

Thyroid and *pituitary substance* may be ingested to the limit of physiological tolerance. This treatment may be supplemented every day or every other day by small doses of *sodium iodid* (gr. 5). Pituitary (anterior lobe pituitary, gr. 1, whole gland pituitary, gr. $\frac{1}{2}$ in capsules) should be administered about the middle of the interval between meals—once, twice, or three times daily, as the case may require. If taken shortly before or directly after a meal, pituitary sometimes causes unpleasant gastro-intestinal symptoms such as colicky pains, nausea, etc. In refractory cases, injection of anterior lobe pituitary (1 c.c. hypodermatically) once a week, may prove of value. The results which follow ingestion of *suprarenal cortex* are disappointing, but preparations of this tissue should be employed when other measures fail. It is prepared in powder and tablet form; the average dosage is gr. 2, twice daily, after meals.

Degenerative changes in the gonads are associated with the following conditions:

Hypopituitarism.—Insufficiency of the anterior lobe of the pituitary of whatever etiology causes hypo-activity of the gonads. Fröhlich's syndrome, dystropho-adiposogenitalis, is a good example. It can be diagnosed by the girdle distribution of fat about the hips, the fat pads about the breasts and above the knees and elbows, the increase of breadth of stature at the expense of height, the small genitalia, and tapering fingers. *x*-Ray examination of the skull invariably reveals a small inadequate sella turcica. While this condition is usually inherited it may result from disease of the pituitary.

Persistent Thymus.—Gonadal disease associated with a persistent thymus evolves into the *thymus-suprarenal-pituitary compensatory syndrome.*

Hypothyroidism.—Hypogenitalism is also associated with cretinoid states. This condition clears up on thyroid feeding.

Senility.—In old age, the testes may become smaller, softer and browner, or harder and more fibrous. The first form is considered normal and in it, while the tubules are narrowed and somewhat thickened, spermatogenesis persists. In the second form there is an overgrowth of fibrous tissue, the epithelial elements disappear, the Sertoli cells persisting longest, and spermatogenesis ceases. Normally, potency should last until the seventieth or eightieth year, sometimes longer. The interstitial cells survive the spermatogenic elements, and therefore libido often outlasts fecundity. In old testicles small scars are often seen, due to obliteration of some of the tubules, and are said to occur more frequently in arteriosclerotics (Davis).

Toxicity.—Any poison capable of producing degenerative changes elsewhere in the body may cause degeneration of the testes. *Alcohol* is said to act selectively on the spermatogenic cells and to leave the interstitial elements unharmed, thus destroying fecundity and preserving the libido.

Irradiation.—Exposure to *x*-ray or radium produces atrophy of the seminiferous tubules without harming the interstitial cells. Prolonged exposure results in complete atrophy of all the testicular elements.

Traumatism.—Degenerative changes may be produced by contusions and wounds which injure the testes directly or damage the blood-supply or vas deferens.

Inflammation.—Degeneration may follow acute or chronic inflammation of the testes or of the epididymis, vas deferens, or seminal vesicles. Infection, the chief causative agent, may enter either by way of the efferent duct or through the blood-stream. *Gonorrhea* most frequently passes by way of the efferent ducts, and all *pus-forming organisms* may enter by this route. Among the *hematogenous infections* causing acute inflammation, are mumps, variola, typhoid fever, scarlatina, influenza, pneumonia, rheumatic fever, pyemia, meningitis, Malta fever, vaccinia, and pyocyaneus.

Chronic inflammation may be due to tuberculosis, syphilis, the mycoses, glanders, leprosy, filariasis, malaria, or echinococcus.

Tumors.—Any metastatic tumor may secondarily involve the testes. Primary tumors of all parts of the testis and its adnexa have been described: these include fibroma, sarcoma, carcinoma, adenoma, lymphosarcoma, and teratoma.

Treatment of the Degenerative Changes.—The treatment is primarily that of the causative condition. Unless complete atrophy has taken place, function should not be considered lost, especially if the subject is young. Spermatogenesis is less likely to be restored than function of the interstitial cells. The treatment outlined for cryptorchidism is helpful in these cases.

Impotence is loss of fecundity without change in the secondary sex characteristics. The libido, while usually modified, is still present. Priapism is infrequent and flabby. Impotence is an adult disease of previously normal males which results from degeneration of the spermatogenic elements without involvement of the interstitial cells. Gonorrhea is the most frequent *cause*. Sexual excess at times produces a somewhat similar condition except that it is really a transient eunuchoid state caused by involvement of both testicular functions.

Treatment.—Administration of *orchitic substance* has proved of little therapeutic value. Treatment should aim for the most part to restore a normal priapism and orgasm so that if any normal spermatogenic elements remain, fecundity will also return. *Pituitary substance*, particularly the anterior lobe, and the *sympathetic stimulants*, such as thyroid, suprarenal gland, and strychnin, are most useful. The dosage must be regulated to the tolerance of each individual.

Eunuchism is complete absence of testicular activity. It is usually an acquired state, as congenital absence or atrophy of both testicles is extremely rare. Accidents or surgical operations are the *cause* of the great majority of cases. *Inflammatory degeneration* is an etiological factor of secondary importance. That *excessive sexual function* is capable of causing this condition is admirably demonstrated by the method of producing eunuchs for certain religious ceremonies among the descendants of the Aztec tribe of Mexico.

"The man, anywhere from twenty to thirty-five years of age, is masturbated several times daily, and made to ride horseback constantly. This treatment soon produces an irritable weakness, so that the act of horseback riding produces ejaculation. Gradually as this régime is continued, the testicles atrophy, the penis atrophies, and the pubic hair may or may not disappear. In addition to this, these men's breasts are suckled by babies, and consequently they develop markedly. The bodily shape is not markedly feminine but remains more or less masculine. The scrotum is shrunken and the testicles are very small and not particularly sensitive to pressure." (Lespinasse.)

Morbid Anatomy.—If castration takes place before puberty, there is a characteristic *skeletal change*. Union of the epiphyses is delayed. The bones of the extremities remain slender but increase in length so that the arms and legs are disproportionately long. The pelvis resembles the female type. Eunuchs are loose-jointed, awkward, and have a tendency to genu valgus. If castration occurs after epiphyseal union, no skeletal change takes place.

The *larynx* remains small and the voice high-pitched and childlike. The voice of individuals castrated after puberty often becomes higher and assumes a shrill quality. The *skin* is pale and soft. That of the face assumes a yellowish, parchment-like appearance and tends to wrinkle. This produces the old and worried look so characteristic of the eunuch. *Secondary sex hair* assumes an undifferentiated character. It is sparse and fine

on the face and chin. Axillary hair is scant and pubic hair is limited to the mons and shows the feminine, horizontal demarcation. *Deposits of fat* about the hips and breasts lend a feminine contour to the figure. The *penis* is small and erections and ejaculations usually are absent. If present, the erection is of short duration and the ejaculation thin and watery.

Morbid Physiology.—Temperamentally, the eunuch is rather quiet and phlegmatic. He lacks aggressiveness and shows a general reversion to the puerile attitude. The eunuchs of Constantinople are avaricious, illogical, obstinate, possess little judgment, and accept information without proof. As a rule, they are fond of children and animals and are faithful in their affections, but possess little courage. Their mentality is often deficient and they are very fanatical. Eunuchs of high intellectual ability, however, are not uncommon.

Treatment.—Administration of orchitic substance is inadequate in the treatment of eunuchism, probably for the reason that no pure extracts of the interstitial cells have been obtained; nor has the active principle of the testes yet been isolated. The feeding of orchitic substance, as it is now available upon the market, is not without benefit in supplementing a mildly decreased testicular function, but is entirely inadequate to supplant a marked or total loss of function.

Tandler reports that a patient who had been castrated at the age of twenty-one continued to practice coitus daily. The erection was of short duration, the orgasm hurried, and the ejaculation thin and watery, but sufficient to permit intercourse. In all other respects, this man was a typical eunuch. Tandler assumes that compensatory activity of the pituitary and adrenal cortex accounted for the persistence of the libido. This assumption is more or less confirmed by clinical evidence which shows that ingestion of pituitary and adrenal cortex improves the mental attitude and allows the patient to approach the various obstacles of his daily life more normally. It may also in part restore the libido. The other eunuchoid characteristics usually change little.

Lespinasse reports the case of a man of thirty-eight who had lost one testicle through a herniotomy and the other through injury, and who subsequently lost the ability to have intercourse. A testicle was transplanted into the rectus abdominalis muscle, and four days after the operation the patient experienced a strong erection and marked sexual desire. Libido remained well marked in this patient for the five years during which he remained under observation. Two of the author's patients with testicular transplants have showed marked improvement for approximately six months; they then relapsed into their former state. Subsequent exploration in one case revealed a complete fibrous atrophy of the transplant. The acquisition of suitable material for transplantation is a problem. In the opinion of the author heterogeneous transplants are not of value.

Eunuchoidismus is the adult form of hypogonadal activity in which the functional elements of the testes are partially but not totally destroyed. The child who manifests lack of testicular activity, either congenital or acquired, continues to be eunuchoid after puberty: likewise, the normal adult suffering partial degeneration of the testes which involves both the spermatogenic and interstitial elements can be considered eunuchoid.

Symptoms.—The clinical manifestations of this condition vary from almost normal to the type in which gonadal activity is so diminished as to

make differentiation from true eunuchism almost impossible. The signs and symptoms of this condition differ only in degree or intensity from those of the eunuch type. Many patients go through life with a mild eunuchoidismus which is perfectly compensated by increased activity of the pituitary and suprarenal cortex; others fail to compensate whenever there is great physical or mental stress; and still others never fully compensate. Such variants tend to confuse the clinical picture of the syndrome, but if the fundamental relations of the sex glands to the pituitary and adrenal cortex are borne in mind, such confusion may be obviated.

Treatment.—The treatment outlined for the eunuch is usually more efficacious for the eunuchoid states. The feeding of *orchitic substance* is of much value in the milder forms. The optimum dosage in the average case is gr. 2, twice daily, four days out of seven.

The Steinach operation is a form of treatment which deserves mention. It was designed particularly to combat the lack of interstitial secretion in senescence, but it is likewise applicable to any of the eunuchoid states. The procedure is simple and consists merely in the ligation of one or both of the vasa deferentia. In experimental animals this operation produces degeneration of the spermatogenic elements and hypertrophy of the interstitial cells, as well as changes in growth and behavior indicative of increased gonadal activity. In his original paper in 1920, advocating the use of this operation for rejuvenating the aged, Steinach cites 2 cases which showed marked improvement following unilateral ligation of the vas.

No comprehensive reports on the use of this method are yet available. The author has never recommended this procedure, and he has seen little benefit from its use. The striking results produced experimentally in lower animals may foreshadow its successful application to man; this, however, has yet to be demonstrated.

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DISEASES OF THE FEMALE GONADS

The ovaries as well as producing the ova determine the formation of secondary sex characteristics in the female. Extirpation of these organs before puberty causes development of an undifferentiated adult with many of the attributes of the eunuch. Extirpation after puberty results in the reversion of the subject to the undifferentiated type without skeletal change. Steinach's classical work on the transplantation of the ovaries in castrated animals is very convincing evidence of the effect of the ovarian secretion on the development of the secondary female sex characteristics. The true luteal structures in these transplanted ovaries degenerate, leaving a preponderance of inner thecal cells and interstitial cells. An internal secretion elaborated by the interstitial cells is probably responsible for the secondary sexual characteristics. This view is corroborated by *x*-ray experiments in which ovulation is inhibited by exposure to the Roentgen-ray. Microscopical examination of ovaries so treated reveals no normal follicles or corpora lutea, yet the secondary sex characteristics remain unchanged.

Menstruation.—It has been known for more than a hundred years that menstruation depends upon the ovaries. Until comparatively recently the ovarian influence was thought to be exerted through the medium of the nervous system. This belief was indeed the basis of the theory of Pflüger, enunciated in 1865, and quite generally accepted for many years. According to this, menstruation is due to a reflex pelvic hyperemia, evoked by afferent impulses from the terminations of the ovarian nerves by the pressure of the growing Graafian follicle. Recent experiments have, however, convincingly disproved this theory, for menstruation or the corresponding phenomenon in lower animals still continues after transplantation of both ovaries into some other part of the body. The ovarian influence is, therefore, hormonic in character.

It is not definitely known which part of the ovary produces the internal secretion essential for menstruation. The weight of evidence is overwhelmingly in favor of the view, however, that it is the corpus luteum; but some authors are inclined to believe that the growing Graafian follicles play the essential rôle. Still others attach much importance to the so-called interstitial cells, although in the human female these are well developed only during pregnancy.

In summarizing the prevailing views of the mechanism of menstruation it may be stated that the corpus luteum, which begins its life history at the time of ovulation, passes through a series of developmental stages which reach the acme just before the onset of the next menstrual period. There is also a similar simultaneous hypertrophic change in the endometrium, which, too, reaches its height just before the onset of the next period. The discharge of blood is indicative of a catabolic or destructive process which takes place in the endometrium when conception does not occur. It is evidence of the transition in the endometrium from the highest to the lowest point of development. If the ovum is impregnated, the hypertrophied endometrium gradually forms the early decidua.

It should perhaps be emphasized that while the corpus luteum is essential for menstruation, it is not, of course, the cause of the actual menstrual hemorrhage. Its rôle is to prepare the endometrium for the possible reception of an impregnated ovum. The actual menstrual discharge begins with the onset of retrogression in the corpus luteum. Although the cause of this has not yet been determined, there is reason to believe that it is associated in some way with the ovum discharged at the previous ovulation. Perhaps the death of this ovum determines the beginning of the retrogressive changes in the corpus luteum and in the endometrium.

DISEASES OF HYPERSECRETION

Precocious Puberty.—Precocity in the female is not unlike that of the male in its etiology and development. It is characterized by the appearance of sex consciousness; the onset of menstruation; the enlargement of the breasts; the rounding out of the hips and thighs; and the development of pubic and axillary hair. Sexual precocity in the female has never been known to be associated with pineal tumor, although pineal shadows are often visible on *x*-ray examination. The condition is not associated with pituitary tumor in either sex. Beekman reports the case of a girl of six and a half years, with large firm breasts, well-developed axillary and pubic hair, an adult type of vulva, and irregular menstruation. *x*-Ray of

the skull revealed an enlarged and eroded sella turcica. The *treatment* and *prognosis* are the same as for the corresponding condition in the male. Special care is necessary to prevent sexual violations.

Hypersecretion in the Adult.—Hypergonadal secretion in the adult female presents a baffling and difficult problem. It is impossible to separate the libido from sexual power as in the male. Exceptional fecundity, as evidenced by numerous pregnancies (15–20) and prolongation of the child-bearing period until between fifty and sixty years of age or more, are evidence of increased ovarian activity. Usually the libido is not increased and treatment is not necessary. Marked increase of libido, nymphomania, occurs most frequently in socially maladjusted individuals, and therefore requires re-education and specialized psychotherapy. A possible source of local irritation should be carefully sought for and, if possible, eliminated. If any endocrinopathy is noted treatment should be adapted to the condition. The causes of this hyperactivity are too varied to permit delineation of any definite rules of treatment.

DISEASES OF HYPOSECRETION

Hyposecretion.—Hypogonadal activity may be due to anatomical anomalies ranging from almost complete agenitalism and pseudohermaphroditism to the presence of a slightly undersized uterus so often associated with dysmenorrhea, or to degenerative changes resulting from disturbances of the pituitary, thyroid, thymus, or suprarenals; senility; intoxications; irradiation; traumatism (including both surgical and accidental); tumors; or infections. The symptoms vary with the age at the onset and the severity of the process.

Complete loss of ovarian function before puberty results in female eunuchism. Menstruation never takes place; the breasts remain undeveloped; there is a tendency to reversive hair distribution; the arms and legs become disproportionately long; the buttocks are lean; and sexual feeling does not develop.

Treatment is of little or no avail in these cases.

The menopause has been described as the time of withdrawal of the internal secretory activity of the ovaries. Sanes reports that the average age at which this phenomenon normally occurs is 47.1 years. Any of the above-mentioned causes may, however, bring on the menopause at any time after puberty.

Symptoms.—Whatever the age of the individual certain symptoms and signs accompany the menopause:

1. *Cessation of menstruation.*

2. *Vasomotor symptoms*, such as flushes, chilly sensations, sweating, vertigo, faintness, vicarious bleeding from any mucous surface, most commonly from the nose, tachycardia, numbness and tingling of the hands and feet, and various types of paresthesia. Novak states that vasomotor symptoms develop in varying degree in 80 per cent. of patients.

3. *Nervous symptoms*, such as excitability, irritability, increased fatigability, emotional instability, and a tendency to worry over little things are not always present, but are not uncommon.

4. *Psychic disturbances* vary in severity from mild depression and phobias to states of active hallucination. The milder forms are not uncommon. Fortunately, the severer manifestations are rather rare.

5. *Anatomical changes* include, in addition to degeneration or destruction of ovarian tissue, atrophy of the subcutaneous tissue of the external genitalia with resultant shrinkage, degeneration of the glandular elements of the generative tract, and diminution and fibrous change of the uterus. The glandular substance of the breasts disappears, and in a large proportion of women there is an increase in body weight.

6. *Diminution or loss of sexual desire* occurs gradually as all the ovarian elements are replaced by fibrous tissue. Frequently, however, in the normal menopause the sexual appetite is preserved, and even at times increased after the cessation of menstruation. This may be explained by the fact that the germinal epithelium disappears before the interstitial elements, which occasionally undergo transient hypertrophy at this time.

Treatment should aim to ameliorate the vasomotor, nervous, and psychic symptoms. *Opotherapy* has proved of great benefit in controlling the unpleasant vasomotor, nervous, and milder psychic symptoms. The real involutional psychoses require psychiatric care as well as organotherapy. *Ovarian extracts* are on the whole the most useful and beneficial. Although some writers favor administration of preparations of the whole gland, the best results probably follow medication with *corpus luteum extracts*, grains 1 to 2 twice daily, four days out of seven, in the earliest phases of the condition. This may be supplemented by injection, subcutaneously or intravenously, two or three times a week, of the liquid extract, which is conveniently put up in ampoule form. Improvement usually follows within the first week of treatment. When fatigability is marked, *suprarenal gland* (grain $\frac{1}{2}$, twice daily), with or without corpus luteum, is of great value. Frequent hypothyroidal symptoms are evident, such as brittleness of the hair and nails, puffiness of the face, thinning of the hair, etc. They should be treated by administration of thyroid to the limit of tolerance. Small doses of sodium iodid (grains 2 to 5, once daily) are also helpful. Pituitary substance (grains $\frac{1}{4}$ to $\frac{1}{2}$, once daily) should always be given at the menopause, for such medication is much better than administration of corpus luteum alone. In the later phases, when the blood-pressure is frequently high, ovarian substance without corpus luteum should be given (grains 5, two or three times daily).

The advantage of *ovarian transplantation* has not yet been demonstrated. Bordier reports rejuvenation of the female at the menopause following *irradiation of the ovaries*, and explains the phenomenon by the occurrence of a transient hypertrophy of the interstitial cells following destruction of the germinal elements which are more susceptible to the *x*-ray. These observations have not been confirmed by other investigators.

Amenorrhea and Oligomenorrhea Due to Hypogenitalism.—"In a much larger proportion of cases than is commonly believed, amenorrhea or oligomenorrhea are the results of endocrine disorders rather than pelvic disease. This is in contrast with the etiology of excessive menstruation, which is to be sought in local pelvic disease far more frequently than in constitutional causes, endocrine or otherwise" (Novak). Varying periods of amenorrhea occur at puberty and near the menopause (physiological amenorrhea), and the condition is normal during pregnancy and the first part of the period of lactation. Failure of menstruation may be due to psychic causes, such as fright, fear of illicit pregnancy in unmarried women, and that interesting phenomenon described as *pseudocyesis*.

Change of climate and environment is at times a cause of transient amenorrhea.

Treatment.—Therapy is necessarily first directed at the cause. *Drugs* are of little value except for an underlying systemic disease such as chlorosis. *Endocrine therapy* yields the best results. Extract of the whole ovary (grains 2 to 5, twice daily after meals) should be administered either by mouth or by hypodermic injection, preferably by mouth as it is often necessary to continue the medication for a considerable length of time. This should be accompanied by pituitary therapy, beginning with small doses (anterior lobe pituitary, grain 1; whole gland pituitary, grain $\frac{1}{2}$, placed in a capsule and given once daily, half way between meals), which are gradually increased (anterior lobe pituitary, grains 2; whole gland pituitary, grain 1, three times a day) if it is possible to do so without producing headaches. The administration of suprarenal cortex is undoubtedly justified in cases of hypogonadal activity. Clinically the results are not as striking as those of ovarian and pituitary feeding, but nevertheless this substance is worth trying in refractory cases. Suprarenal cortex is prepared in powder and tablet form: the dose is grains 2, by mouth, twice daily, after meals. Opotherapy in amenorrhea or oligomenorrhea, regardless of the cause, should not be employed while the patient is acutely ill.

Primary dysmenorrhea is menstrual pain not associated with any demonstrable form of pelvic disease. The causes are mechanical obstruction of the cervical canal; neuritic factors; and hypoplasia of the uterus. The last two undoubtedly depend upon an underlying endocrine factor in a large percentage of cases.

Symptoms.—The typical neurotic type of patient often gives the following history: The periods usually occur early (every twenty-one to twenty-six days) and for a week or ten days before onset, the patient is nervous, excitable, depressed, apprehensive, and gives way to tears on the slightest provocation. Often tachycardia occurs, and slight enlargement of the thyroid gland. Fatigue is a common symptom. The onset of menstruation is accompanied by great weakness, sometimes nausea and vomiting, severe cramp-like abdominal pains, backaches, and cramps in the muscles of the legs. The patient is usually confined to bed for the first day or two, and sedatives may be necessary to control the pain. Careful examination often reveals signs of hypofunction of the thyroid, suprarenals, and pituitary alone or in combination. Furthermore, the frequency of menstruation is a manifestation of inadequate secretion of the corpus luteum.

Treatment.—If *gynecological measures* fail *organotherapy* may be employed. The following régime often proves beneficial. A week or ten days before menstruation is due, according to the time of onset of the nervous symptoms, corpus luteum should be administered, usually grains 2, by mouth, twice daily. This should be continued until the first day of menstruation. During the remainder of the month the underlying glandular deficiency should be counteracted by small doses of thyroid, suprarenal, or pituitary as the case may be.

Dysmenorrhea associated with hypoplasia of the uterus does not respond so satisfactorily to treatment. In some instances, especially in young subjects, glandular therapy is beneficial. Growth of the uterus should be promoted. The type of ovarian and pituitary therapy is similar to that of the neurotic conditions. In addition subcutaneous injection of the liquid

extract of the anterior lobe of the pituitary (in doses of ½ to 1 c.c. two or three times a week) is advisable.

FUNCTIONAL UTERINE BLEEDING

(*Idiopathic or Essential Uterine Bleeding*)

No local pelvic disease can be demonstrated in functional uterine bleeding. This condition usually reveals itself as metrorrhagia, or more often as menorrhagia, and occurs most frequently at the time of puberty or near the menopause. The nature of the disturbance and the time of occurrence seem to indicate that it results from some type of endocrine disturbance, the nature of which is not yet clear. Novak believes that it is due to a disturbed ovarian function.

Treatment.—*Opotherapy,* more or less empirically used, has at times proved of benefit. In general, thyroid therapy is most satisfactory at puberty, while corpus luteum therapy proves most helpful at the time of the menopause. There are, however, numerous exceptions to this rule. Pituitary therapy, especially injection of pituitrin, at times proves of value. Unfortunately the treatment of this condition is still a matter of trial and error, and no definite rules can be laid down.

It is not a good plan to administer *lutein* regularly without intermission. Usually, to conform more or less to the natural processes, it should be omitted for one week in every four, the week during which normally there is no lutein secretion. Conditions resembling anaphylactic shock, acidosis, and allied states are at times produced by too continuous use of lutein.

Walter Timme.

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Diseases of the Male and Female Gonads

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INFANTILISM

Definition.—Infantilism properly includes all degrees of arrested development from the almost complete type described by Lorain to the presence in an otherwise normal individual of a dimple in the chin, a maxillary torus, or the absence of a lateral incisor. It is often classified as universal and partial, but the dividing-line is difficult to define. If organs remain in the state normal to intra-uterine life (patent foramen ovale, cleft palate, coloboma, etc.) it is often spoken of as embryonalism or fetalism.

Etiology.—Disturbances of the sympathetic nervous system and of that part of the endocrine system concerned with the regulation of growth are responsible for the condition. The underlying causes are of two types: hereditary defects in the germ plasm, probably in the chromosomes themselves; and destructive lesions, either infectious, chemical, or physical, of the nervous or endocrine system in the growing organism.

Strauch makes the following classification according to etiology:

1. Infantilism due to true endocrine diseases.

(*a*) Myxedema and cretinism (thyreogenic).

(*b*) Absence or under-development of the genitals (dysgenitalism).

(*c*) Disturbances of the hypophysis.

(*d*) Disturbances of other glandular structures, such as the thymus, parathyroids, suprarenals, pancreas.

(*e*) Pluriglandular infantilism.

2. Dystrophic infantilism with:

(*a*) Status thymicolymphaticus.

(*b*) Angioplasia.

(*c*) Valvular lesions (congenital, or acquired early).

(*d*) A history of intoxication and infection in the parents, such as chronic alcoholism, saturnism, mercurialism, morphinism, pellagra, malaria, tuberculosis, leprosy, and other endemic diseases.

(*e*) Congenital lues and extra-uterine diseases, such as tuberculosis, typhoid, severe chronic intestinal insufficiency, interstitial nephritis, cirrhosis of the liver, etc., which are acquired very early.

(*f*) Diseases of the brain (trauma).

(*g*) Degeneration due to unhygienic conditions or to deficient nutrition.

(*h*) No detectable cause; primary defectiveness of the germinal cell; heredity.

According to symptoms infantilism may be grouped as follows:

1. Morphological infantilism.
2. Biochemical infantilism; lack of resistance to fatigue and infection.
3. Psychical infantilism; irresponsible, distractible, superficial, lack of concentration, low intelligence quotient; behavioristic and emotional low levels.

Manifestations.—Detailed description or even complete enumeration of the many various forms of infantilism is here impossible. The fact that any tissue or function may be affected, either alone or in combination, makes possible the occurrence of innumerable variants. One type which most closely approaches the universal and most nearly embodies all the characteristics of the other forms deserves detailed consideration. It was first described by Lorain in 1871.

The Lorain Type of Infantilism.—In the Lorain type of infantilism, development is so uniformly arrested that the relative proportions are preserved. Von Rosthorn's classical description of the condition is approximately as follows: growth is diminished, the skeleton is graceful and of childish proportions, viz., the lower extremities are short; the typical curvings of the vertebral column are only slight; the pelvis is hypoplastic and of lessened inclination; the hips are narrow; the facial skeleton is underdeveloped, for the chin and jaws are hypoplastic and the nose is infantile; and the mastoid processes are small. The musculature is poorly developed; the nates are flat; and the growth of hair scanty. Typical alterations are evident in the genitalia; in the female the external parts are barely covered by the flesh of the thighs as in normal woman, and the internal parts show typical hypoplasias; the funnel-shaped vulva is suggestive of the original urogenital sinus; in the male the testes and penis are small but well formed, in contrast to those characteristic of the eunuchoid and hermaphroditic states; a scrotal fold frequently surrounds the base of the penis. There are developmental anomalies of the kidneys, cecum, and lower end of the intestinal tract, not demonstrable clinically. The total picture of the general habitus includes also the infantile heart, the narrowness of the circulatory system, and frequently, during puberty, a disturbance of the correlation of the organs responsible for the integrity of the blood tissue. Finally, the psyche is infantile.

Diagnosis.—The diagnosis of infantilism is not difficult and depends upon lack of development of any organ or tissue. The differentiation of types is more of a problem because the varieties are so intermingled. Type depends upon the outstanding feature of the condition. When the lack of development is uniform it should be classified as the Lorain type.

Treatment.—Individuals with infantilism are chronologically adults, though morphologically children. After puberty treatment is of little value; when instituted before this stage, however, it may be beneficial. Patients should be carefully examined for any infection or intoxication and properly treated for any such disturbance. The general rules of hygiene (a properly balanced diet, fresh air, sunshine, proper rest and recreation, and efficient elimination) should be observed. Opotherapy should be instituted: as no two cases are alike, each must be treated according to its needs. Ad-

ministration of thyroid and pituitary substances by mouth, to the limit of tolerance, proves useful in a large number of cases. It is of great importance to determine by all possible means (clinically, as well as through laboratory examination) the points in which the patient is underdeveloped in order to discover the most suitable forms of therapy.

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DISEASES OF THE SPLEEN

It has long been known that the spleen is not an organ necessary for life; in fact the ancients, on the erroneous supposition that the speedy giraffe did not possess a spleen, are said to have excised the spleen of runners, in order to increase their efficiency. Although since the time of Malpighi, clinical and experimental investigations of splenic activities and functions have been numerous and ingenious, it is only recently that concise concepts of its function have been obtained. The author has attempted to assemble these in an article in the Physiological Reviews.

As an important member of the hemolytopoietic system, the spleen is unquestionably concerned intimately with blood-cell formation and destruction. Like the liver it may easily revert to its embryonic function of forming leukocytes and erythrocytes, as occasion demands, and it continuously forms lymphocytes and monocytes in common with other tissues. Blood-cell formation is also controlled indirectly by the spleen through its influence on the bone-marrow. Whether or not blood-cell destruction begins within the circulation by fragmentation or by hemolysis the spleen is in either case directly concerned. The fact that phagocytosis of cell débris or, if necessary, of whole cells takes place not only in the spleen, but in the other parts of the reticulo-endothelial system, explains the rapid accommodation that occurs after splenectomy. The spleen is probably also indirectly concerned with destruction of blood in other ways. The clinical importance of this function, especially when it is increased by disease, is shown by the great diminution in the destruction of blood that follows splenectomy in hemolytic jaundice and pernicious anemia.

The majority of the evidence clearly points out that the spleen plays a rôle of clinical importance in relation to immunity. It has a selective affinity for bacteria, fixes toxins, and produces antibodies; but here also the spleen co-operates with other tissues which can quickly assume these functions after its removal. Its frequent involvement in infections is a clinical demonstration of this important relationship, and the serious lesions that may result are examples of the common biological phenomenon that on sufficient provocation an organ may become the chief victim of the very process which it is designed to combat. Its relation to tumor growth is also im-

portant. Grafts in the spleen "take" less frequently and are smaller than elsewhere, and intrasplenic inoculation is most successful in raising resistance to tumor grafts elsewhere in the body. Removal of the spleen also seems to stimulate the growth of tumors and to diminish resistance.

Secondary involvement of the spleen is important in many diseases, whereas its primary diseases are few. It will, therefore, be necessary to mention briefly the splenic features of various diseases that are treated more fully elsewhere.

Anomalies.—In a few cases the spleen has been found to be completely absent, usually when there are other anomalies. It may be subdivided into numerous splenunculi; or a normal spleen may be accompanied by one or more accessory spleens. These usually share in its pathological changes, and should, therefore, be removed with the spleen. In the present incomplete state of our knowledge, some very small and very large spleens which are normal except for size are best considered as anomalies. Abnormalities of position are usually due to or associated with other congenital defects; deviations from the normal shape are seldom of clinical importance.

Movable Spleen.—A movable spleen (*floating spleen, lien mobile*) may be found in any part of the abdomen. Osler quotes that one was found in an inguinal hernia. Such a spleen may become fixed in the abnormal position by adhesions, and present great difficulty in diagnosis. Such a condition is either part of a general enteroptosis (Glénard's disease) or follows the enlargement of chronic splenic disease. *Symptoms* may be absent or general (especially digestive or circulatory), and may be referred chiefly to some other organ that has been disturbed. If the shape and notches can be palpated, *diagnosis* is easy. The absence of the normal splenic dulness and the fact that the mass can be returned to the normal position of the spleen are also of diagnostic aid. *Treatment* is usually desirable to forestall complications. If a belt and pad or bandages prove unavailing, operation is necessary. Either splenoplexy or packing in position with gauze to induce the formation of adhesions is desirable; and even splenectomy may be advisable if the spleen is diseased.

Torsion of the pedicle is a complication of *lien mobile*, which usually causes acute violent symptoms demanding immediate surgical relief. Sudden pain and enlargement of the spleen with signs of shock, and often fever and vomiting, are the characteristic signs. A partial or more gradually produced twist causes less severe symptoms.

Rupture.—Traumatic rupture of a normal spleen is possible, although this accident is usually found to occur in an organ that is diseased. Rupture occurs fairly commonly in malarial splenomegaly, and may take place spontaneously during acute typhoid fever, when malaria has caused enlargement, or after torsion of the pedicle. The *symptoms* resemble those of torsion with signs of internal hemorrhage. Rapidly increasing anemia and a marked leukocytosis may ensue. *Surgical treatment* is, of course, imperative. If secondary to an infarct or abscess, the symptoms of the primary cause are added and signs of general peritonitis soon develop.

In a series of 5000 autopsies performed at the Philadelphia General Hospital between 1920 and 1926, the spleen in one instance was replaced by several splenunculi varying in diameter between 1 and 3 cm. No case of movable spleen, torsion, or rupture was encountered.

Congestion and Acute Splenic Tumor.—On account of the peculiar anatomy of the spleen, as well as its functional relation to infections and toxemias, congestion occurs frequently. The passive congestion of chronic heart failure produces the familiar "cyanotic induration." The acute splenic tumor of infectious diseases is the commonest pathological lesion of this organ. The spleen is probably enlarged in all acute infections of sufficient severity, frequently to the extent of being palpable.

Abscesses of the spleen are usually multiple, are relatively rare, and usually result from the breaking down of a septic infarct. "In rare instances the whole organ may be converted into a sac of pus" (Osler). More rarely abscesses may follow such infectious diseases as typhoid, malaria, phlebitis, and erysipelas. Of the 9 cases in our series the infection was transmitted by the blood-stream in 7, by extension in 2. The *symptoms* are often subordinated to those of the primary source of the trouble until rupture and general peritonitis ensue, or the condition may not be discovered until autopsy. Sudden local pain and tenderness, sometimes associated with a characteristic friction-rub of perisplenitis, and the usual signs and symptoms of severe suppuration may permit *diagnosis*. *Laparotomy* is then indicated.

Infarction of the spleen occurs much more often than is recognized clinically. It was found 202 times in the series of 5000 autopsies (140 anemic, 62 hemorrhagic), but had undoubtedly occurred in many of these cases without causing symptoms or requiring special treatment.

If caused by a sterile embolus, the infarct is simple and anemic and is followed eventually by fibrosis and shrinkage. Not infrequently, however, a fresh hemorrhagic infarct is found at autopsy. An infected embolus causes a *septic infarct*, rich in micro-organisms, with a characteristic serpiginous border, and frequently terminating with the formation of an abscess. It is much rarer than the simple infarct; indeed this type was noted only four times in our series. A correct *diagnosis* is often difficult. The commonest *symptom* is local pain, especially if perisplenitis develops, with tenderness over the somewhat swollen organ; but, as has already been mentioned, some acute splenic tumors, partially twisted pedicles, or abscesses also cause these symptoms. *Surgical intervention* is not required unless continued chills and septic fever indicate the formation of abscesses. The treatment otherwise is that of the underlying condition.

Chronic Splenomegaly (*Amyloid Spleen, Cirrhosis, Tuberculosis, Syphilis, Malaria*).—The various forms of chronic splenomegaly have certain pathological features in common. There is generally an early congestion and hyperplasia, with obscuration of the Malpighian follicles, followed later by atrophy and fibrosis. Splenomegaly also plays an important part in such conditions as the leukemias, pernicious anemia, Hodgkin's disease, rickets, and kala-azar, to which sections the reader is referred.

Amyloid Splenomegaly.—Amyloid disease of the spleen is of clinical interest on account of its possible confusion with other types of chronic splenomegaly. Caused by the same chronic conditions no matter what its location, amyloid disease occurs more frequently in the spleen than in any other organ (156 times in the series mentioned, as compared with 83 times in the liver, and 78 times in the kidney). When the enlargement is *diffuse*—the "Sago spleen" involvement of Malpighian follicles being of pathological interest only—the spleen may attain an extreme size and cause considerable disturbance by dragging, or by pressing on surrounding organs. *Diagnosis*

is aided by the manifestations of a chronic disease elsewhere and by the signs of amyloid change in other organs (digestive disturbances, enlargement of the liver, urinary changes, etc.). The *treatment* consists in general hygienic measures with the main effort directed against the primary disease.

Cirrhotic splenomegaly is not infrequently such a prominent and early manifestation of hepatic cirrhosis that it produces special symptoms, and is even thought by some to contribute to the cirrhotic process in the liver or at least to be due to the same toxic cause. This is probable not only on account of the "upstream" relation of the spleen to the liver in the portal circulation, but also because successful removal of the spleen improves existing anemia and lessens the amount of ascites and collateral circulation. Whether or not the obstruction to the portal circulation is the sole underlying cause, enlargement of the spleen quickly becomes hyperplastic as well as congestive, and according to Eppinger's theory of hypersplenism may well bring about an excessive destruction of erythrocytes and a consequent moderate or severe anemia.

Syphilis of the spleen may be either diffuse or, much more rarely, gummatous, and may occur either congenitally or as an acquired disease. *Diagnosis* depends on the combination of an otherwise unexplained splenomegaly with the signs or history of syphilis, a positive Wassermann reaction, and a marked anemia, and tendency to jaundice and ascites. *Treponema pallidum* has occasionally been found. Although ordinarily part of the general luetic process and to be treated accordingly, syphilis of the spleen sometimes demands independent recognition. In certain cases when the spleen continues to be enlarged and causes discomfort, and when the positive signs of general syphilis remain after adequate treatment, the question of splenectomy arises. As in syphilis of the central nervous system, the virus sometimes seems to be so protected (in a by-path, so to speak) that it withstands specific treatment and maintains an active focus of infection. Successful removal of the spleen in such cases has permitted further treatment to become efficacious.

Tuberculosis of the spleen, although a common secondary infection (606 out of 5000 cases), occasionally, like syphilis, forms a resistant focus from which further infection is disseminated. The spleen may be greatly enlarged by extensive infiltration with caseated or fibrotic tubercles, or may rarely be the site of a single, palpable, nodular tuberculoma—often when no tuberculous lesions are demonstrable in other organs. According to Winternitz, this "primary" type attacks both sexes equally and at any age, but is most often seen in patients from twenty to forty years of age. In 70 per cent. of 51 cases reviewed, pain and swelling of the organ were found, usually with chronic digestive or respiratory disturbances, fever, weakness, and emaciation. If tuberculosis is present or develops elsewhere correct diagnosis should often be possible. On the other hand, the acute type of tuberculosis manifested by collapse, fever, chills, and backache, and the atypical forms, present great diagnostic difficulty. Except for the rather high postoperative mortality, splenectomy is a satisfactory form of treatment.

Malaria of the Spleen.—This disease, like tuberculosis and syphilis, may also produce splenomegaly. The spleen apparently becomes a reservoir which resists specific treatment and permits the continuance of the disease. In malaria, as in kala-azar, the spleen, because of its very

function of destroying red blood-cells, is exposed to infection by the organisms which it liberates. The large, hard, pigment-laden spleen of chronic malaria need not be described here. Attention should, however, be called to the numerous and complex adhesions, which greatly increase the difficulties of removal. Nevertheless, splenectomy has been followed by a constantly decreasing mortality, and the patients who survive are greatly improved.

Tumors of the spleen, although rarer than in most abdominal viscera, are probably more common than is generally recognized. The benign type—fibroma, lymphangioma, and hemangioma—is of little or no clinical importance. Of the malignant tumors, sarcoma, lymphosarcoma, and endothelioma may be primary, whereas carcinoma is always secondary. According to Smith and Rusk, 184 primary tumors of the spleen have been reported in the literature. Of the 23 secondary malignant tumors of Krumbhaar's series, the primary cancer was in the breast in 5 cases, the pancreas in 3, the stomach in 3, the lip in 1, the prostate in 1, and in the penis in 1; 4 were melanosarcomata secondary to skin lesions, 3 were lymphosarcomata, and 2 endotheliomata of lymph-nodes. Tumors of the spleen are formed both by direct extension and by metastasis through the blood and lymph-stream. *Diagnosis* is usually made too late to permit practical treatment, although a certain number of primary tumors have apparently not recurred after removal. Pain and a steadily growing mass in the left abdomen, with rather quickly developing anemia and emaciation, are the traditional signs, but these are by no means always present.

Cysts of the spleen may be simple (congenital or acquired), parasitic or neoplastic, and single or multilocular. *Simple cysts*, whether the result of trauma, infolding of the peritoneum, dilatation of lymph-spaces, breaking down of hematomata, necrosis, or infarction, are comparatively rare. Fowler has seen 98 non-parasitic cysts, and Lombard and Duboucher have recorded 158 encysted hematomata. Splenic cysts are most commonly found in women of child-bearing age and the acquired types are thought to be usually associated with trauma. When sufficiently large to attract notice the cysts usually appear as a slowly growing mass in the left hypochondrium, and cause soreness and a dragging sensation. Fluctuation of the mass is, of course, an important sign, and a diagnosis can be made in some cases by tapping. *Parasitic cysts* (echinococcus) need not be discussed here. *Neoplastic cysts* are almost curiosities; only 2 dermoid cysts have been reported, but angiomata occur more frequently. Splenectomy is accomplished easily, has never been reported to be fatal, and should be performed if the symptoms warrant it.

Thrombosis of the splenic vein may be either partial or complete, and produces symptoms that are acutely fatal or persist for many years. It may be due to trauma, extension of nearby infection, pressure from tumors or adhesions, and many other causes.

Symptoms.—As a result of the blockage, the spleen becomes greatly congested and enlarged (600 to 1000 gm.) and the current in the gastric veins (*vasa brevia*) may be reversed (*i. e.*, toward the stomach). This is apt to cause the copious and recurrent gastric hemorrhages which are such prominent symptoms. In acute thrombosis, sudden abdominal pain, pallor, weakness, and signs of collapse may precede a fatal gastric hemorrhage. In the chronic form, there is frequently a recurrence of abdominal

symptoms for several years; there are obvious gastric hemorrhages, or occult blood is present in the stools; and there is a tendency toward jaundice. The spleen becomes palpable in spite of the accompanying ascites, and the anemia and leukopenia are often disproportionately severe. It is this combination which makes the differentiation of true *Banti's disease* so difficult. If the thrombosis involves the mesenteric veins, hemorrhoids will be added to the picture; and if the portal vein is involved, *caput medusæ* and other signs of collateral circulation appear. The symptoms may, on the other hand, be obscure and confined to gradual abdominal enlargement, so that pre-operative diagnosis is nearly impossible. *Diagnosis* is always difficult and is seldom made before death. If a correct diagnosis can be made, *splenectomy* should be performed.

Splenic Anemia (*Banti's Disease, Splenomegaly with Anemia, Splenomegalie Primitive, Splenomegaly with Hepatic Cirrhosis*).—Definition.—Splenic anemia is a chronic disease of unknown origin, probably toxic, and primary in the spleen, and is characterized by splenomegaly, anemia, and leukopenia, a tendency to gastric hemorrhage, increased function and destruction of blood-cells, and later by cirrhotic changes in the liver, with ascites and jaundice. The term "Banti's disease" is sometimes reserved for the late stage of the disease.

History.—The term "splenic anemia" was first used over sixty years ago by Gretzel in describing a case of chronic enlargement of the spleen and marked anemia without leukocytosis in a child. Through the articles of H. C. Wood, Sippy, Osler, and many others, this term gradually became familiar, but included a variety of conditions. In 1883, Banti mentioned that cirrhosis of the liver and splenic anemia occurred together, and eleven years later he described fully the condition that still bears his name.

Etiology.—Banti thought that the noxious agent was brought to the spleen by the splenic artery either as a direct toxin or as a substance which was there converted into a "splenotoxin." In his original paper he emphasized the absence of contributing infections, intoxications, alcoholism, irritating food, etc. Of the various micro-organisms that have been thought from time to time to play an etiological rôle, none are recognized today. Except for the better understanding of related conditions, therefore, there has been no advance in the study of this problem for many years.

Morbid Anatomy.—The morbid anatomical changes are not especially distinctive. The greatly enlarged spleen in early cases may show increase in the reticulum with a cellular, hyperplastic pulp and degenerative changes in the follicular arterioles. Later the follicles become small and scarce as fibrosis of the reticulum, trabeculæ, and capsule increases. Hemorrhages and infarcts are not uncommon. The lymph-nodes are normal, the bone-marrow hyperplastic, and the liver (in the third stage) shows an ordinary periportal cirrhosis.

Symptoms.—The disease usually begins in young, otherwise healthy adults of either sex, and if untreated proves fatal after several years. Banti divided its course into three periods: the first, anemic or pre-ascitic; the second, intermediary; and the third, cirrhotic. In the *first*, which is the longest period (two to four years or more), a gradually increasing weakness and pallor are noticed, as well as the digestive disturbances and abdominal discomfort, which may first call attention to the enlarged, smooth, hard spleen. The anemia is moderate, the resistance of the red blood-cells is slightly in-

creased, and there are few or no signs of active formation of blood. Neutrophilic leukopenia is characteristic, although leukocytosis may occur after hemorrhage or intercurrent infection. Hemorrhage, usually from the gastric veins or esophageal varices, is not uncommon. It may be fatal, moderate and chronically recurrent, or so slight as to be detected only by the presence of occult blood in the stools.

The *second*, or *intermediary stage*, according to Banti, lasts only a few months, and is characterized by increased digestive disturbances, diarrhea, hemorrhoids, and a red, turbid, scanty urine. It is doubtful if this stage can be recognized.

The *third stage* is ushered in by the symptoms of cirrhosis and recurrent, painless ascites, with occasional jaundice and increased anemia and emaciation. The urinary changes are more marked, and urobilin is present in increased amounts in the urine and feces. With marked terminal exhaustion, fever and cardiorenal troubles are not uncommon. After several months or a few years an intercurrent infection or hemorrhage causes death.

Diagnosis.—The diagnosis of splenic anemia is necessarily made chiefly by exclusion. The various splenomegalies mentioned, like *hemolytic jaundice* and *Gaucher's disease*, have more or less distinctive signs; and when the liver is cirrhotic a careful history of the order of appearance of symptoms must be relied upon to demonstrate the primary trouble. The age of onset, the leukopenia, and the chronicity are the guiding features of the disease. *Hanot's cirrhosis*, which often develops in even younger individuals, is differentiated by the large liver, the greater tendency to jaundice and hepatic symptoms, the abdominal crises, and leukocytosis. *Pernicious anemia* in the stage of remission, *aleukemic stages of leukemia*, and *atypical Hodgkin's disease* may present difficulties which usually disappear on prolonged study.

Prognosis.—Spontaneous recovery is unknown. Exacerbations may alternate with minor impairment of health for varying periods of time, until in the third stage definite invalidism supervenes.

Treatment.—If the operative risk is not too great *splenectomy*, even in the third stage, is the only logical treatment. In preparation for this, or if operation is inadvisable, the usual hygienic and medicinal measures should be utilized. *Transfusions* are valuable if the anemia is severe or after dangerous hemorrhage. If ascites is troublesome and diuretics prove useless, *paracentesis* may be necessary. *Talma's operation* (omentopexy) may be combined with splenectomy if cirrhosis and ascites are already present.

Gaucher's Disease (*Large Cell Splenomegaly*).—Definition.—Gaucher's disease is a rare condition characterized by chronic anemia and a marked splenomegaly, due to peculiar large vesicular cells, which are also found in other parts of the hemolytopoietic system.

Etiology.—First described by Gaucher in 1882 as a primary epithelioma, the changes were later shown to be a unique form of endothelial or reticular cell hyperplasia, the cause of which is still unknown.

Morbid Anatomy.—Although the cells typical of the enlargement can be found histologically in bone-marrow, lymph-nodes, and liver, they are most abundant in the spleen. This organ is greatly enlarged (average 3600 gm.), smooth, brownish red, and, when cut, the normal landmarks are found to be obscured or invisible. There are occasional minute hemorrhages or

infarcts. Histologically the characteristic cells are round and large (17–40 micra or more in diameter), with one or more small nuclei, and much pale, faintly acidophilic cytoplasm which does not contain fat or lipoids, but does contain iron compounds. In Niemann's disease, a more acute and rare variant, the affected cells do react to lipoid stains.

Symptoms.—Gaucher's disease begins insidiously in infancy or childhood, usually before the thirteenth year, and pursues a very chronic course (average of twenty years). The enlargement of the spleen, which may reach enormous proportions, is sometimes discovered accidentally or as the result of local symptoms, or else the anemia with its train of symptoms may be the first to become apparent. The tendency to hemorrhages, submucous or subcuticular, the anemia, and leukopenia are all less marked than in Banti's disease. The liver may be considerably enlarged in advanced cases, though jaundice and ascites are rare. The superficial lymph-nodes are not enlarged. A brownish discoloration of the skin has been noticed with a "peculiar yellowish wedge-shaped thickening of the conjunctivæ, commonly seen on both sides of the cornea."

Diagnosis.—While diagnosis is usually made on pathological material, the family history, early onset, great chronicity, size of the spleen, and pigmentation of the skin may afford the clue. Several times the correct diagnosis has been discovered by splenic puncture, a procedure that is not without danger.

Prognosis and Treatment.—Splenectomy is the only procedure that has proved of value. As the operative mortality is still rather high and the disease very chronic, the operation should not be attempted without considerable thought. If the operation is successful the chances for improvement are great, although as the disease coincidentally attacks other parts of the hemolytopoietic system, complete cure is hardly to be hoped for. If its progress outside of the spleen is sufficiently slow, however, the improvement may be lasting.

Hemolytic Jaundice (*Congenital, Familial, Acquired Jaundice, Hemolytic Splenomegaly, Chronic Family Jaundice, Acholuric Hemolytic Icterus with Splenomegaly, Cholémie Familiale, Anemia Ictero-hemolytica*).—Definition.—Hemolytic jaundice is a chronic disease, primarily due to increased destruction of blood-cells and characterized by anemia, increased fragility of erythrocytes, acholuric icterus, and splenomegaly.

History.—First observed by Murchison in 1885, hemolytic jaundice was established as a clinical entity by Hayem in 1898. Widal's emphasis on the exacerbations or "crises of deglobulization" led to designation of the acquired form as the *Hayem-Widal type*. Two years later Minkowski recorded its familial occurrence; and after Chauffard called attention to the fragility of the erythrocytes, which is its essential feature, the familial form became known as the *Chauffard-Minkowski type*. This name also includes the isolated congenital cases. An excellent review of the subject has recently been published by Tileston.

Etiology.—The *acquired form* may be secondary to some acute infection (malaria, tuberculosis, syphilis, dysentery, cholangitis), but in many cases the cause cannot be determined. The *congenital or familial* disease is believed to be hereditary, though syphilis and tuberculosis of the parents are thought to be predisposing causes.

Morbid Anatomy.—The excessive blood destruction causes deposition of blood pigment throughout the hemolytopoietic system. The spleen is

greatly enlarged (500 to 1500 gm.), and the pulp and sinuses are much congested. The bone-marrow is hyperplastic, if the anemia is sufficiently severe. Gall-stones, probably due to inspissation of the increased bile secretion, are common.

Symptoms.—Splenomegaly is often the first sign of the disease. The size of the spleen and the abdominal discomfort increase during exacerbations. The *jaundice* is distinct, but not intense, and is not associated with clay-colored stools or with the presence of bile pigments in the urine, *i. e.*, it is non-obstructive. Urobilin is present in urine, stools, or duodenal contents in greatly increased amounts, constituting an important diagnostic sign.

The *anemia* varies greatly in different cases, tending to be more marked in the acquired form of the disease. The patient may be "more icteric than sick" (Chauffard), or may be incapacitated by an anemia that verges on the pernicious type. In the familial type of hemolytic jaundice the red blood-cell count averages over 3,000,000, whereas in the acquired disease it is about 2,000,000; in 10 recorded cases it was below 1,000,000. The quantity of hemoglobin is proportionately low; anisocytosis is marked; and microcytes are especially common. The resistance of the red-cells to hypotonic salt solution is greatly lowered. The number of reticulocytes is greatly increased (up to 15 or 20 per cent.).

In the exacerbations, which are especially marked and characteristic when the disease is acquired, the patient may suddenly become seriously ill with fever, abdominal pain, increased jaundice (non-obstructive), leukocytosis, and increased anemia.

Diagnosis.—The decreased resistance of the erythrocytes is practically pathognomonic. The blood findings and acholuric jaundice should also aid in the differentiation of other forms of splenomegaly, although the hemolytic type of pernicious anemia may present difficulties. The presence of gall-stones should not be allowed to mask the condition.

Prognosis.—The danger to life is slight except in the exacerbations of severe cases. In most instances, however, the damage to health is considerable.

Treatment.—*Splenectomy* has proved, almost without exception, a practical cure, which brings quick and permanent relief of symptoms. With the improvement in the recognition of the disease and its operative treatment the mortality has now fallen below 3 per cent. Even this low death rate should suffice, however, to prevent surgical intervention if the patient suffers little or no inconvenience. While the blood-count rises to normal, the jaundice disappears and the excretion of urobilin diminishes; the resistance of the red cells usually increases but fails to become normal.

Before treatment of the acquired form careful search must be made for the underlying cause. If this can be removed, the symptoms of hemolytic jaundice may also disappear. If splenectomy is performed, it is advisable to remove any chronic foci of infection at the same time. Splenectomy should practically never be performed during an exacerbation.

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DISEASES OF THE LOCOMOTOR SYSTEM

Diseases of the Muscles

FIBROSITIS

(*Muscular Rheumatism, Myalgia, Myositis*)

Fibrositis is regional or general inflammation of the connective tissue of the fasciæ, aponeuroses, sheaths of muscles and nerves, ligaments, tendons, periosteum, and subcutaneous tissue.

History.—The disease has been little known and ill described. William Balfour of Edinburgh first described the definite fibrous thickenings to which Froriep later drew attention. The term fibrositis was first applied to this condition by Sir William Gowers in 1904.

Etiology.—Localized infection with non-pyogenic organisms is probably the chief etiological factor, although exposure to cold, wet, muscular strain, or trauma may be predisposing causes.

Morbid Anatomy.—The lesions which involve the white fibrous tissue in the muscles, joints, and peripheral nerves consist of inflammatory hyperplasia of varied degree. In this new tissue many fibroblasts can be seen, and also evidence of inflammation in the blood-vessels and nerves. A serous or serofibrinous exudation is present. The older the inflammatory tissue becomes, the more fibrous and more permanent it is apt to be. The resulting indurations may cause thickening in large areas which contain many painful spots. On palpation these are hard, inelastic, and slightly brawny. Sometimes they are circumscribed and vary in size from that of a split pea to that of an almond; or they may be felt as a thin cord in the fascia or subcutaneous tissue. They are very tender on palpation.

Symptoms.—If the fibrositis is due to exposure, the symptoms begin within a few hours and continue to be acute for three or four days. The condition is, however, more apt to begin less acutely and produce *pain* as the most prominent symptom. This is either constant or excited by movement. It may be dull and continuous, or sharp and shooting. Occasionally it is so severe and cramp-like that it makes the patient cry out. The pain lasts for a few hours, a few days, or for weeks. It tends to recur. *Stiffness of the joints* and a tendency to muscular fatigue are associated with the pain. If the muscles of the head and neck are involved, the nodules may give rise to the so-called *indurative or nodular headache*. Lumbago is the name given this affection when it is in the lower back. If the muscles of the anterolateral or back region of the neck be concerned, a *stiff neck* or torticollis ensues. *Pleurodynia* results from involvement of the chest muscles. The lesions may invade any or all parts of the body and produce pain, stiffness, tender areas of induration, and varying degrees of disability.

Treatment.—Careful search for a local focus of infection should always be made. The affected part must be put at rest and protected from the cold. For lumbago, acupuncture and cauterization are advised. Heat and

any form of counterirritation are also efficient. Salicylates relieve the acute pain; potassium iodid is useful in more chronic conditions. Massage is always helpful.

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MYOSITIS

Definition.—Myositis is inflammation of the muscles. The condition has long been recognized, but has never been satisfactorily classified. Altogether, Lorenz's division of the various types seems to be the most serviceable yet presented. He limits his classification to those types which are primary; it must not be forgotten, however, that inflammation of the muscles is often a secondary disturbance in many infectious diseases. The myositis of tuberculosis may be primary, but is of rare occurrence.

Primary Suppurative Myositis.—DEFINITION.—Primary suppurative myositis is either a single or multiple inflammation of the muscle, which is usually acute and of bacterial origin. Ordinarily it presents the clinical picture of an acute infectious disease.

HISTORY.—The first well-defined case was described by Foucault in 1869. Twelve years later Micaise observed another case. Suard and Brumon then made a special study of the condition; and Lorenz a few years later reviewed all the reports and rejected all but eleven cases as atypical. Since then the disease has been seen in other countries.

INCIDENCE.—This type of myositis appears to be most common in Japan, where Miyake claimed in 1904 that 250 cases had been reported. *Myositis purulentia tropica* has been described by Ziemann, Appel, and others as a tropical disease in Africa, and seems to be related to the primary suppurative type. Children were previously considered most susceptible to the primary suppurative disease, but further observation has shown that *age* bears no relation to the incidence. *Sex* also appears to make but little difference, although the disease is more common among men of the laboring classes. This can probably be explained by the fact that they are more subject to trauma and overexertion, factors which play an important rôle in the etiology of myositis.

ETIOLOGY.—Fujiy claims that most of the cases develop among laborers who work in the fields, and are, consequently, exposed to undue cold and fatigue. Overexertion and trauma also seem to favor the onset of primary myositis.

MORBID ANATOMY.—Three types of primary myositis have been recognized: (1) that manifested by large solitary abscesses in the muscles; (2) that associated with disseminated abscesses in the muscles; and (3) that in which diffuse purulent muscular infiltration takes place. The first variety is by far the most common. The skin and underlying tissues of patients

with this disease may appear normal, but the muscles undergo extensive change. They become dark-red or grayish in color, edematous, and very friable. The abscess itself contains thick yellowish pus mixed with blood and particles of tissue, and its walls are lined with gray or yellowish-gray necrotic fibers. When the tissue is examined under the microscope, the changes can be seen to be serous, seropurulent, or purulent in character. The connective tissue may be hypertrophied and extensively infiltrated with mononuclear and polymorphonuclear cells. The muscles show evidence of hyaline, granular, and fatty degeneration; the nuclei are somewhat increased in size and the sarcolemma sheaths thickened. Masses of bacteria can be seen near the walls of the abscess. When the condition is chronic and a large amount of granulation tissue has formed, new muscle-fibers are produced by direct nuclear division.

Symptoms.—The onset is usually sudden. A chill is followed by fever without other evidence of disease. In some cases there may be *prodromal symptoms*, such as general malaise, profuse perspiration, anorexia, headache, and pains in the extremities. After the *fever* has set in, an ill-defined pain begins which soon becomes localized in the implicated muscles. These before long become swollen, indurated, and very painful. Edema of the overlying tissues, and ecchymosis or erythema, may develop in extensive areas. Within ten days the swelling shows signs of fluctuation, and an abscess may be found which should be opened immediately to prevent the formation of multiple abscesses. The inflammation rarely progresses to resolution. One or more muscles may be involved. The lesion usually begins in a single or multiple focus and then spreads. Recurrences may occur at intervals of three or four months.

Diagnosis.—The swelling of the muscles associated with dense infiltration, fluctuation, and pain usually makes the diagnosis easy. If there is still doubt, an incision should be made into the swollen muscle.

Prognosis.—The outlook is favorable if the necessary surgical treatment is given early. In Miyake's series of 33 cases there was only one fatality. Muscular atrophy may follow healing of the abscesses. Severe contractures are occasionally observed during the period of healing which may last for from one to three months.

Treatment.—Cold and other antiphlogistic agents should be employed in the early stages of the disturbance; but if abscesses have formed it is necessary to make a broad incision to permit thorough drainage of the pus. Contractures should be treated by massage and various orthopedic measures.

Non-suppurative Myositis (*Dermatomyositis*).—Definition.—Dermatomyositis is an acute, subacute, or chronic disease of unknown origin, which begins gradually with vague prodromal symptoms, and is characterized by edema, dermatitis, and multiple inflammation of the muscles.

History.—The disease was not recognized clinically until 1887, when Wagner, Unverricht, and Hepp simultaneously reported cases. Since then the incidence has increased markedly.

Incidence.—Sex and season seem to have no influence upon the occurrence of this type of myositis. Only 1 case has been reported in a negro, and the Anglo-Germanic race seems to be the most susceptible. The individuals most often attacked are in the prime of life and in the best of health.

Etiology.—The cause is still unknown, but most investigators believe that the disease is infectious. Cold and fatigue appear to play a part in the etiology.

Morbid Anatomy.—The lesions are limited to the muscles and the spleen. Any or all of the muscles may be involved. The skin over the muscles involved assumes a characteristic hardness and does not pit on pressure in spite of the usual slight edema. On section, the subcutaneous tissues appear edematous and infiltrated with a yellowish serous fluid which renders them firm. The muscles are swollen, pale red or yellow in color, infiltrated with serum, and either hard and firm or soft and boggy in consistency. They undergo all degrees of degeneration and are coarsely or finely granular, hyaline, waxy, or rarely fatty. In size they are normal or small. Longitudinal or cross cleavage and vacuolar degeneration have also been observed, as well as round-cell infiltration in the perivascular connective tissue and between the muscles. In chronic cases the quantity of the connective tissue is much increased.

Symptoms.—The onset is usually slow, and manifested by such symptoms as anorexia, malaise, or pain in the extremities, which may persist for as long as three weeks. The *pain* is at first vague, but soon becomes definitely localized in the muscles. It may involve different groups of muscles successively until the whole musculature of the body is attacked. The pain rapidly becomes more and more severe, and is increased by active or passive movement. It is drawing, tearing, or boring in character and may force the patient to go to bed. In the later stages peculiar cramp-like pains are common. On palpation, the muscles are found to be very tender. Contractures have been occasionally reported. The *edema* which develops simultaneously with the *fever* may spread over the entire body and the extremities; it is usually first noted above the eyelids or in other portions of the face, and gives the countenance the appearance of alabaster, according to Oppenheim. The swelling most often involves the proximal parts of the extremities, leaving the wrist and ankle joint normal. It is asymmetrical, hard or soft, and may be localized in the affected parts or spread to surrounding parts. *Dermatitis,* which is usually an early symptom, is of most varied character; pseudo-erysipelas may develop, and urticaria, roseola, erythema, eczema, or an eruption resembling erythema nodosum. It may remain localized where it first appears or spread over the entire body; almost invariably it develops over the diseased muscles. The dermatitis may disappear and leave no trace, or produce pigmentation of the skin where it has occurred. The *fever* is usually moderate, and may be intermittent or remittent. *Profuse perspiration* and *enlargement of the spleen* are also common symptoms. The *urine* is usually normal. *Paresthesia* as revealed by a feeling of formication has been described by four observers. The *knee-jerks* and *electrical reactions* may be either normal or diminished. In subacute and chronic cases improvement may alternate with relapses which last from a few months to a year or a year and a half. Acute cases last for from one to two weeks to two months.

If there are interstitial hemorrhages between the muscles, or if circulatory symptoms develop, the syndrome of dermatomyositis assumes a special character which was first differentiated by Lorenz. He reported 5 cases of this disease which he termed *polymyositis hemorrhagica*. Prodromal symptoms are usually lacking, and the onset is more sudden than

in the more common type. The fever, too, is less severe, and the duration is generally several months. Nephritis is a usual complication.

Diagnosis.—If the symptoms be kept clearly in mind this disease should not be difficult to diagnose. *Scleroderma* has in one instance been confused with it.

Prognosis.—In a series of 28 cases collected by the writer, 17 proved fatal. The outlook is, therefore, unfavorable. Death may result from suffocation produced by involvement of the muscles of respiration and deglutition, or from bronchopneumonia.

Treatment.—Rest in bed is essential. Thermomassage has been recommended, and Oppenheim suggests that it be followed by massage, gymnastic exercises, and electrotherapy. The pain may be relieved by aspirin, pyramidon, the salicylates, or, when more severe, by morphin.

Myositis with Special Terminal Lesions.—Primary Myositis Fibrosa.—*Definition.*—Primary myositis fibrosa is a single or multiple muscular inflammation which may be either subacute or chronic. It usually begins in the lower extremities and causes slight constitutional symptoms. The muscles involved undergo marked atrophy, and are eventually replaced almost entirely by connective tissue. Gies reported the first case in 1878 and termed the condition *myositis chronica;* Volkman later considered it a separate clinical entity.

Etiology.—No specific cause has been discovered; and no definite agents seem to increase the susceptibility of individuals to the disease.

Morbid Anatomy.—The muscles at first swell and assume the appearance of tumors. On palpation they are found to have a wood-like or sand-bag-like consistency which is very characteristic. A dense edema may develop in the skin and underlying connective tissue. These do not pit on pressure. The muscles grate on the knife when being cut and in section appear white when most seriously involved, reddish yellow when the lesion is less advanced. Connective tissue eventually replaces the muscle-fibers. Atrophic fibers can also be found, as well as those which have undergone hyaline or vacuolar degeneration. The transverse striations may be lost, but the longitudinal markings are often increased. The relative quantity of tendinous tissue also increases.

Symptoms.—The onset of the disease is usually slow, and the disturbance is first noted in the muscles of the lower extremities. Only one muscle or a single group of muscles is involved. The *pain* in the muscles implicated soon becomes so severe that the patient is forced to go to bed. Because of the rigidity of the muscles attacked, troublesome contractures may develop, especially in the flexors. Most of the voluntary muscles may eventually be involved. The *electrical reaction* of the muscles may be reduced or lost. The *sensation* is very rarely disturbed.

Diagnosis.—Certain diagnosis is possible only after histological examination of the tissues, but the wood-like hardness of the muscles, and the fact that pain is slight or lacking on palpation are said to be characteristic of the disease. This type of myositis persists for a long time, but in spite of periods when there is no change decided improvement eventually takes place.

Treatment.—Drugs are of little therapeutic value, but massage and electricity are helpful if properly employed.

Progressive Myositis Ossificans.—*Definition.*—Progressive myositis ossificans is a progressive inflammatory disturbance of the locomotor sys-

tem, characterized by the gradual formation of bony masses in the fasciæ, muscles, aponeuroses, tendons, ligaments, and bones, with eventual ankylosis of most of the articulations. The first full description of the disease was made by Freké in 1740, but Rosenstirn states that Guy Patin mentioned a case in a woman in 1692.

Etiology.—The cause is unknown.

Morbid Anatomy.—According to Rosenstirn the lesion first develops in the connective tissue of the exoskeleton and spreads to the tissues of the endoskeleton. The condition should, therefore, in his opinion be termed *fibrocellulitis ossificans progressiva.* The disease generally develops in young adults; and it is usual for women to be attacked at an earlier age than men. Men, however, are more susceptible.

The pathology of the diseased muscles was first thoroughly studied by Hawkins in 1844. Thirteen years later Minkewitsch again investigated the disease, but the syndrome did not become recognized as a clinical entity until Munchmeyer published his famous article in 1869. He described three stages of the disease—embryonic infiltration, connective-tissue induration, and ossification. In the *first stage*, the skin and subcutaneous tissue may appear normal, but the underlying muscle is swollen and edematous because of extensive infiltration of the connective tissue both within and between the muscles, which results from the formation and proliferation of connective tissue. This may be seen most markedly about the blood-vessels. In the *second stage* this embryonic tissue becomes organized into adult connective tissue which at first proliferates and then contracts into a hard fibrous mass. This on section has the appearance of a fibroma and contains remnants of muscle-fibers which appear as red striations on a white background. Before the fibers are completely destroyed fatty, waxy, and granular degeneration takes place, most markedly at the center of the hard white masses. The nuclei of the sarcolemma increase in size, and the connective tissue contains cells which vary from the fusiform type to the large polymorphous variety. The latter frequently contain karyokinetic figures. Non-capsulated cells which resemble those of cartilage appear at this stage. In the center of the fibrous masses spaces soon develop which represent osteoid trabeculæ and contain cells which later form osteoblasts and bone corpuscles. When these become calcified the parts enclosed by trabeculæ form bone-marrow. The *third stage* ensues when ossification results in the formation of compact and spongy bone. The new bone which develops similarly in the fasciæ, ligaments, tendons, and pre-existing bones is fibrous, cartilaginous, or periosteal in character, and resembles normal bone in every respect.

Symptoms.—At the onset of the disease the symptoms vary very greatly and are often quite characteristic of rheumatism until the third stage is reached. Occasionally signs of myositis are absent, but typically the diseased muscles are always swollen and have a doughy consistency. The *pain* may either be localized in the muscle or radiate to other parts. As a rule there is *edema* of the overlying tissues, some redness of the *skin*, and slight *fever*. These signs disappear after a period of a few days, but the *induration* of the muscle persists so that the tissue resembles a tumor and may contain deposits of bone. Rarely the mass disappears as muscular degeneration sets in, and very infrequently the muscle returns to a healthy normal state.

If bone is formed in the original lesions the process usually persists for from two to eight months, and may involve the entire muscle, its fleshy portion, or its tendons. The formation of bone is usually painless, but the patient may be disturbed by spontaneous pains, especially at night. The muscles of the back and neck most frequently undergo the first change, while those of the upper and lower extremities and of the face are involved in order. When the cervical ligaments and neck muscles become ossified the head is flexed and fixed. Ossification of the ligaments, fasciæ, and muscles of the back produces various changes; if localized in a muscle free movement may be possible, but if it spreads the muscles become firmly attached to the skeleton. The lesions have been compared to the ramifications of coral, to the mountain-ranges on a map, and to a stag's antlers. The process gradually spreads until the vertebral column becomes fixed. This produces a scoliosis which, in extreme cases, causes the lower ribs to touch the iliac crests. Kyphosis develops much less often. When the pectorals and latissimus dorsi become involved the arms are rigidly fixed on the thorax, which has been described as a bony coat of mail. Involvement of the upper extremities usually precedes that of the lower. Marked contractures develop in both. Eventually the hips become slightly flexed; the arms are fixed at the shoulder and flexed at the elbow. This, and the forward projection of the head, produces a precipitous gait in walking. The forearms, hands, legs, and feet are rarely involved. If the temporals, masseters, and pterygoids are attacked the lower jaw cannot be moved, and patients can be fed only after removal of some of the teeth or of a portion of the alveolar process of the lower jaw.

Exostoses may form on the inner surface of the arm, the anterior aspect of the tibia, the upper portion of the fibula, on the ribs, or where the long bones approach the skin. They have also been observed on the frontal bones and on the phalanges of the fingers. These may later disappear. Another peculiar anomaly which is found in about 75 per cent. of the cases is a deformity of the great toes and thumbs and occasionally of the little fingers; this was described by Gerber and later pointed out by Helferich. Before the use of the *x*-ray it was generally supposed that the deformity was due to absence of one phalanx; but it is now known to be caused by stunting of the growth of the metatarsal and metacarpal bones and subsequent ankylosis of the interphalangeal joints. Generally the great toes are directed outward; often they lie under the second toes and thus produce the deformity known as *hallux valgus*. The condition may be noted at birth or may develop later. An absence of certain muscles and atrophy of the testicles and scrotum have also been seen in isolated instances.

The *diagnosis* of advanced cases of this disease is not difficult; in the early stages the presence of exostoses, microdactylia, bony deposits in various parts of the body, and the progressive character of the lesions should leave little room for doubt.

Prognosis.—The outlook is not hopeful, although periods of cessation and recurrence of symptoms may alternate for years. Eventually the subject becomes helpless and bedridden. Bed-sores and abscesses about the bony deposits give added discomfort. Death may result from pyemia or some intercurrent infection. If the costal limitation be marked and edema of the glottis ensue the patient may be suffocated.

Treatment.—There is no medical treatment for the disease. Surgical

removal of the bony deposits is not beneficial because in every instance the deposit has recurred after operation. If the lower jaw becomes fixed, some of the teeth must be removed to permit introduction of food through a tube. Trauma and cold should be avoided as they seem to favor spread of the disease.

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Diseases of the Joints

Chronic Arthritis

Definition.—Chronic arthritis is a term used to describe any chronic inflammatory condition of the joints, or of the periarticular structures. Chronic arthritis manifests itself clinically in a variety of forms which are dependent upon different etiological factors.

Occurrence.—Diseases of the joints constitute the oldest form of pathological disturbance of which we have any record. Arthritis and the so-called rheumatic disturbances occurred even during the Stone Age, and there is ample evidence that they affected many forms of life before man existed. At the present time rheumatism probably occurs more commonly and is more wide-spread than any other disease to which human beings are subject.

Until recently this cause of suffering and disability has not been accorded its full importance, but it is probable that in the near future more attention will be paid to its prevention and treatment. Arthritis and rheumatism may develop in individuals in nearly any state of health, but they very often attack those who seem perfectly well.

Although the incidence of these disturbances is highest during the middle or later decades of life, there are certain well-recognized conditions, such as Still's disease, which characteristically attack children and adolescents. *Sex* as well as *age* seems to affect the susceptibility of individuals to these disturbances. Of a series of 500 patients 66 per cent. were women, the majority of whom were between forty-five and fifty years of age. The incidence also seems to vary among different races. In this country negroes are less frequent victims than whites.

Etiology.—The infectious nature of many arthritic and rheumatoid conditions remained obscure until about twenty years ago, although there is ample evidence that in certain isolated cases its nature was suspected much earlier. In fact, even Hippocrates referred to the rôle of focal infection; and Benjamin Rush in 1819 cited a case in which this was clearly the cause. But at present the great importance which is attached to the rôle of such localized infections in the etiology of rheumatic disorders has withdrawn attention from other factors which should receive consideration. Attacks of influenza, empyema, furunculosis, or almost any inflammation of bacterial origin are known to precipitate arthritis and rheumatism; and any conditions which tend to reduce the general well-being of the individual are at least a contributory, if not in themselves the direct, cause of the development of these abnormalities. Recent studies of arthritis and rheumatism in the American Army during the World War demonstrate that exposure of various kinds was the immediate cause in 60 per cent. of the cases. This corroborates the old popular idea that cold and wet are aggravating factors. Whether the well-recognized influence of the intestinal tract upon these disorders depends upon its relation to metabolism or upon the infections which it may harbor is not yet definitely known. The action of the endocrines is also questioned, but the temporary improvement which sometimes follows such emotional disturbances as worry, grief, anger, or the excitement incidental to travelling, points to some connection between this complicated system and the rheumatic syndrome. It is doubtful whether arthritis and rheumatism are ever hereditary. These disorders, however, are particularly apt to develop in individuals of the enteroptotic build which is hereditary.

The most fully understood as well as the most emphasized cause is infection. This is usually so localized and inconspicuous that the patient is quite unaware of it. The nose and throat are the most common site of such trouble. Even when the tonsils are buried and apparently small they may be grossly infected. The teeth come next in order of importance, chiefly in relation to apical abscesses and gingivitis. Disorders of the genito-urinary tract, although of less importance, must not be overlooked; they are less often causative of arthritis in women than in men. A boggy prostate may set up wide-spread disturbances. The causative infection is not always restricted to these regions, but may occur in the sinuses, gall-bladder, or any other part of the body. There is no doubt that many, and probably most, cases of arthritis and rheumatism are in some way closely related to such focal infections at some stage, especially when the patient is below middle age.

The infectious organisms may be of many kinds, but in general one of the numerous strains of *Streptococcus* predominates. To *Streptococcus viridans* is accredited the greatest importance, although the *Streptococcus*

hemolyticus, the *Pneumococcus*, the *Staphylococcus*, or the *colon bacillus* may all produce similar results. The gonococcus is the cause of a clinically distinct type of arthritis which probably does not differ fundamentally from the more usual forms.

Sometimes the causative organism can be cultured from the affected joint, but this is infrequently the case. It seems probable that the infecting organism, when actually the cause of the disease, may also operate through its influence upon the endocrine system and the factors concerned in the mechanism of defense. A theory of elective affinity on the part of various organisms for certain tissues or structures has been advanced by some workers.

Pathology.—There are few diseases in which the late manifestations are more obvious than in rheumatism and arthritis, but since the external evidences depend entirely upon the location, intensity, and character of the pathological processes no single lesion can be described as typical. Lesions may develop in muscle, tendon, ligament, cartilage, or bone, and may appear during the early stages of the disease.

In the muscles, fibrositis may develop either early or late, but it eventually becomes sufficiently pronounced to be obvious, permanent, and characteristic. It consists of interstitial round-cell infiltration and subsequent proliferation of the connective-tissue cells. The newly formed connective tissue separates, compresses, and finally in large measure replaces the muscle-fibers, which eventually undergo marked atrophy. The fibrous investments of the muscles, the tendons, the nerve-sheaths, and even of the fatty tissues may also be involved.

It is in the joints, however, that the lesions are most striking. Statistics show that the knee is the point most frequently attacked and that the hands are next in order. In one group of patients arthritis involved the knee in 67 per cent. of the cases, the hand in 63 per cent. In the army, the figures were 62 per cent. for the knee and 14.5 per cent. for the hands. The knee is probably most susceptible because it is one of the weight-bearing parts. The lesions may vary from a slight inflammatory thickening of the soft tissues to erosion, dislocation, and deformation, and even locking of the joints. Fibrositis, which appears early in the ligamentous structures and articular capsules, causes swelling and limitation of motion and eventually thickening, contracture, or even fibrous ankylosis of the moving parts.

Of the many classifications of the types of arthritis the simplest and probably the most comprehensive is that of Nichols and Richardson. They divide all the arthritides into two types, the proliferative and degenerative. Although their classification is open to some objection, it seems justified by the fact that all the lesions found, even in such conditions as "Charcot's Joint," appear to be the result of either proliferative or degenerative processes.

Proliferative arthritis[1] is generally characterized by swelling of the soft tissues, especially in the smaller joints, and by ultimate subluxation or ankylosis. The fingers, for instance, may become sausage-shaped while the pathological processes are active, and later assume a dimpled appearance on the dorsal surface as the disturbance subsides. The first evidence of this type of arthritis is an overgrowth of the synovial membrane or perichondrium, which is at times accompanied by involvement of the under-

[1] Sometimes called *atrophic* arthritis.

lying osseous structures. This produces a granulation tissue or pannus, which spreads over the cartilage and other structures within the joint cavity and destroys them. The somewhat specialized form of connective tissue which is also formed may later change into cartilage or even bone. Thus destruction and proliferation may occur simultaneously. In the later stages the destruction of cartilage leads to union of the bones, which may eventually be so complete that the two marrow cavities merge. This condition is known as *true bony ankylosis*, and is often simulated by the apparent immobility caused by rigidity and contraction of the fibrous tissues.

The degenerative type of arthritis,[1] on the other hand, usually entails more irregular deformity of the bones and less change in the soft tissues. It never results in true ankylosis, or in the locking of fingers in an extended position. The first change is a fibrillary degeneration which softens and erodes the hyaline cartilage and exposes the underlying bone. This process may continue until the bones of the joint meet. As the lesion is rarely symmetrical, however, and as there is frequently "compensatory" proliferation of the cartilage or bone of the opposing surface of the joint, irregular contact usually results. Friction between the opposing surfaces renders the bone smooth, polished, and eburnated. The increased activity of the perichondrium at the periphery of the joint results in the formation of new cartilage and finally new bone, and thereby irregularly enlarges the size of the head of the bone. Perhaps the most common manifestations of these changes are to be seen in the terminal joints of the fingers, which become bulbous on one or both sides. These enlargements are known as Heberden's nodes. The view that this type of arthritis never seriously involves other more important joints is doubtful and probably unjustified. While true ankylosis or bony union is never associated with this type of arthritis, motion may be much restricted; indeed, joints may be almost locked by projection of their margins and by subluxation.

In both types of arthritis subcutaneous fibrous nodules frequently develop. They appear usually along the tendons of the fingers and around the smaller joints of the hand, but may be distributed all over the body, especially in children. With convalescence they generally disappear.

The processes just described constitute in some degree a vicious cycle, because the abnormal position and contact of the joint surfaces cause mechanical trauma, which further modifies or aggravates the existing conditions; and also because loss of motion is followed by profound changes in the metabolism and nutrition of the parts involved, even when they are at rest. Many metabolic aspects of arthritis have been studied, but without clear-cut results. It may be said, however, that investigation has indicated that there is in arthritis at least a local, if not a systemic, disturbance—probably a retardation—of metabolism. The changes in the bones can be explained on the basis of chemical processes, and there is abundant clinical evidence that they depend upon variations in some of the fundamental metabolic processes of the body. Observations made on soldiers in the United States Army show that in a majority of cases of arthritis the sugar tolerance is lowered, just as it is during other types of inflammation. This is in no way specific, but is good evidence of a systemic disturbance. The following changes in metabolism were also noted—the basal metabolism was slightly subnormal in 20 per cent. of the patients

[1] Sometimes called *hypertrophic* arthritis.

observed; the quantity of creatin in the blood was slightly increased in about half of the cases studied, and there was a tendency toward a retention of salt and water in the body. Although for generations both physicians and the laity have insisted that nitrogenous foods, especially "red" meats, are harmful to arthritics, the urea and nitrogen contents of the blood remain normal. There are indications of a slightly subnormal blood-flow in arthritis and rheumatism, and studies of the blood-gases afford evidence of difficulty in the utilization of oxygen, especially by the peripheral tissues.

It is of the highest importance to appreciate that while the morphologic changes above described constitute the most graphic evidences of the rheumatic process, they are merely symptoms of a fundamental dynamic disturbance, and that the eye, the peripheral nerves, the central nervous system, and the skin may also be subject to physiological abnormalities.

Clinical Course and Symptoms of Arthritis.—Inasmuch as the external evidences of arthritis depend entirely upon the location and intensity of the pathological processes, there is no single clinical picture typical of the disease, but there are a few symptoms and signs which commonly precede or accompany its onset. Muscular cramps, twitching, and various forms of paresthesia, such as numbness and tingling, often appear before any of the more obvious symptoms of arthritis and cause much discomfort. A sensation that the arm or hand is asleep frequently wakes patients at night. Various psychoses, such as depression, melancholia, or even insanity, which result from the influence of the specific toxin upon the central nervous system may be manifest before arthritis is distinct, and often seem to be independent of its course. In many cases marked displacement of the abdominal viscera, such as ptosis of the kidneys, spleen, stomach, intestines, and even of the liver, precedes the onset of the disease itself, but it must be borne in mind that such conditions may also result from the loss of abdominal musculature and from the incorrect posture which accompanies many types of arthritis.

The actual onset of chronic arthritis may be very abrupt and violent or so gradual as to escape detection. In some cases it simulates the onset of acute inflammatory rheumatism, while in others, there are exacerbations quite comparable to attacks of this acute disease. Usually, however, the onset is gradual. Because of previous susceptibility to stiffness of the muscles after exposure to a draught, or to lumbago of purely muscular origin, many patients may have regarded themselves as mildly rheumatic long before arthritis really developed. In the majority of cases, however, symptoms of moderate severity first appear in some joint, such as the knee, ankle, or knuckle. The first manifestation may be a slight stiffness, with or without pain upon motion. This may be recurrent or continuous, and when severe is accompanied by redness, heat, and swelling of the soft tissues, and sometimes by an effusion into the joint. This is easily observable when it occurs in the knee. The margins of the joint are usually tender to pressure. Throughout the entire course of the disease, but especially during the early stages, *fatigue* is the most marked and often the most distressing symptom. *Neurasthenia* is common, especially in individuals of enteroptotic build.

Certain secondary changes are common to all types of arthritis. If a joint is not used on account of pain or stiffness, the muscles which should move it atrophy because of disuse. Inflammation, such as the so-called fibrositis already mentioned, aggravates this loss of muscle tissue; wasting

may become so marked as to be noticeable on casual observation, and may be accompanied by tenderness of the muscles to palpation. As atrophy progresses, movement of the joint becomes increasingly difficult and a vicious cycle is established. When the legs are thus involved the general health is impaired. Loss of appetite, loss of weight, and abnormalities of metabolism result from restriction to a sedentary life, and are sooner or later followed by secondary anemia and asthenia almost as severe as that attributable to frank infection with the streptococcus and analogous organisms. In the arthritides of bacterial origin, which are frequently accompanied by a slight *leukocytosis*, the white count may be raised to 11,000 or 12,000 or more. In one series of observations the white count was over 11,000 in 19 per cent. of the patients. Except for the low red count, there is, however, no constant differential change in the blood.

As arthritis progresses the *blood-pressure* tends to fall as a result of the abnormally quiet life of the patient and the loss of vascular tone occasioned by decreased muscular contraction. In a group of 177 patients between ten and eighty years of age the average systolic pressure was 127 mgm. of Hg, the diastolic 73, in spite of the fact that 119 individuals were over forty years old. In many cases this reduction may be much more marked, *i. e.*, systolic pressure may fall to 100 mgm. Hg. There are types of arthritis, however, which are accompanied and even preceded by an increase in the blood-pressure. They appear most frequently in rather stout women of middle age and belong to the degenerative group. Low blood-pressure causes the pulse rate to rise. Slight, continuous fever is frequently associated with the bacterial arthritides.

In contrast to acute inflammatory rheumatism, arthritis rarely injures the *heart* directly. It is probable, however, that the factors which favor arthritis may also favor arteriosclerosis and a low grade of myocardial degeneration. If cardiac lesions occur during arthritis they are usually of minor importance.

When the patient is confined to a chair the *feet* tend to become *edematous* because of poor circulation and their low position. In many cases profuse sweating of the hands and feet, either with or without exertion, is a marked feature. The extremities are generally cold, subjectively as well as objectively, and the nails somewhat cyanotic. Trophic disturbances may render the nails brittle and striated until they finally assume the thickened condition known as paronychia.

The *skin* often is sensitive to the touch and assumes a glossy appearance as arthritis becomes established. Although the apparent association of dermatoses with arthritis has not been fully explained, the incidence of various types of skin disease in any large group of arthritic patients is noteworthy. Psoriasis is probably the most frequent.

Neuritis and *neuralgia*, which are common manifestations of the rheumatic syndrome, often cause much suffering. Sciatica is perhaps the most severe of these disturbances, and may be caused not only by true inflammation of the peripheral nerves and their sheaths but also by such mechanical factors as sacro-iliac subluxation.

Headache is a common symptom. While it is generally of moderate intensity, it may reach the severity of migraine. Various ocular disturbances also occur, such as iridocyclitis, and general disease of the uveal tract which is probably closely related to the same general process.

Certain arthritic syndromes have come to be regarded as definite clinical entities, and must, therefore, receive separate mention here. Severe *spondylitis* produces two distinct types of disturbance: one of which is characterized by marked symptoms of nerve-root involvement; the other by extension of the pathological processes to the hips and shoulders. Von Bechterew, who has described the former type, believes that it begins as a meningitis, which causes compression of the nerve-roots and loss of function of the paravertebral muscles; and that it leads to ankylosis of the entire spine. The symptoms are referred pain and anesthesia in the back of the chest. In this form of arthritis the essential pathological change is alleged to be an ascending degeneration of the spinal cord. In the latter type (Spondylose rhizomélique) the nervous symptoms are less marked and the abnormalities are proliferative in character.

If spondylitis can be arrested during the preliminary stage when only the ligamentous and muscular tissues are involved, structural deformities may not be great; but when the intervertebral cartilaginous disks atrophy, and projecting overgrowths extend downward from the bodies of the vertebræ and fuse with those below, the entire spine may become ossified. In such cases expansion of the thoracic cage is soon prevented by fixation of the attachments of the ribs both posteriorly and to the sternum. Respiration consequently is abdominal. This syndrome yields very reluctantly to treatment.

Another distinct type of arthritis is *osteo-arthritis*, which is characterized by hypertrophy of bone and involvement of the large proximal joints. This is rarely acute, and although it may cause very severe pain disturbs the general health comparatively little. The muscles atrophy during the early stages. Such mono-articular arthritis chiefly affects old persons, though it may occur at any age. When it develops in the hip it is often referred to as *morbus coxæ senilis*. Injury may be a precipitating factor.

Still's disease is regarded as another distinct syndrome, but is probably nothing more than the manifestation of rheumatism and arthritis in children and adolescents. It is usually accompanied by fever and marked lymphatic enlargement. The spleen is, however, usually enlarged. The disease may interfere with normal development and leave the child in poor condition.

In *intermittent hydrarthrosis* there is periodic swelling of one or more joints without fever. The effusion, which may take place rapidly, is accompanied by stiffness, but not necessarily by pain. The intervals between attacks may vary from a few days to several months. Many disturbances supposed to be of this type are probably of arthritic, angioneurotic, or anaphylactic origin. In some instances attacks are accompanied by edema of the face or erythema. Generally the disease cannot be arrested.

So-called *villous arthritis*, in which there is a proliferation and enlargement of villi within the joint, should also be mentioned. It seems to be static in origin in many cases and not infrequently referable to flat-foot. The local crepitation and pain of varying degrees upon movement are generally not accompanied by systemic symptoms.

Diagnosis of well-established arthritis and rheumatism is not difficult, but early diagnosis demands very careful observation and examination. Rheumatic "lumbago" may be closely simulated by strains, faulty posture, sacro-iliac subluxation, tuberculosis, or even malignant disease of the spine.

Diffuse muscular pain and discomfort caused by obscure arthritic conditions may be unjustly ascribed to neurasthenia. Gout and arthritic disturbances are sometimes mutually confused, but can usually be distinguished by means of the localization of the lesion and by the formation of tophi or pultaceous areas characteristic of gout. There is, however, an increasing acceptance of the suggestion that the two diseases are not entirely separate. In the United States gout is very rare as compared with arthritis. Bursitis in the shoulder or elbow occasionally causes symptoms which cannot be distinguished from those of arthritis unless the lesions are sufficiently advanced to be differentiated by *x*-ray examination.

Although practically useless as a means of diagnosis in the early stages of the disease, *x*-ray examination demonstrates in nearly all advanced cases the pathological changes characteristic of arthritis.

The **prognosis** of arthritis has greatly improved during the last fifteen or twenty years as the various causes, manifestations, and modes of treatment of the disturbance have come to be understood. Physicians are slowly learning that no single measure suffices to arrest the disease or to abolish deformities, and that only by intelligent combination of the various therapeutic methods available can the active pathological processes be inhibited and the patient restored to activity. As a result of such treatment, there is no longer justification for the idea that *rheumatoid arthritis* and *arthritis deformans* are incurable and progressive.

The severity of the disturbances depends not a little on their localization. Locomotion is less affected, of course, by lesions in the arms than in the legs, and consequently the general health suffers less when the disturbances are confined to the arms. Pathological processes in the knee, which may be violent though of brief duration, may produce, within a few weeks, deformities which only the most persistent and skilful treatment can remedy. If not suitably cared for they prevent physical activity and eventually cause invalidism. In some types of arthritis the pathological changes spread from one joint to another. The fingers, for example, are first attacked, then the wrist or shoulder. When the spine is involved, the ankylosis may cause almost complete rigidity and distressing deformity. In practically all cases of arthritis, however, deformity may now be prevented by adequate care. Even when ankylosis is inevitable, it can usually be secured in the position of greatest physiologic and economic value. Orthopedic advice is often invaluable to this end. Although the underlying causes of the rheumatic syndrome do, sooner or later, specifically affect the condition of the body as a whole, arthritis *per se* is rarely the cause of death. Not infrequently operation to remove the apparent cause proves fatal in advanced cases, but death is more often caused by such intercurrent diseases as influenza and pneumonia to which feeble patients are particularly susceptible.

The **treatment** of arthritic and rheumatoid conditions is still very difficult and unsatisfactory in spite of the advances which have been made during the last fifteen years. The measures advocated as beneficial are legion, and it has been stated that their very multiplicity is proof of ineffectiveness. This is far from correct, however, for the treatment of these disturbances must necessarily be varied—the causative agent must be removed, the general health improved, and the actual lesions cured in so far as possible and rendered painless.

Removal of the Causative Agent.—Perhaps the most signal improve-

ment in treatment dates from the recognition of the relation of rheumatic disorders to infectious processes of various kinds, especially to so-called focal infections. In the past, attempts to cure arthritis by removal of such infections have sometimes led to operations which have left the patient worse rather than better, and it is still often difficult to determine whether or not in any given case the disease is really the result of localized infection. In general, however, it is desirable to remove all possible causes of trouble. Consequently a very thorough examination of arthritic patients is necessary, for there is great difficulty in detecting the less conspicuous foci. The *x*-ray may demonstrate the presence of abscesses at the apices of the teeth, but does not do away with the necessity for further examination by a competent dentist. Apparently sound molar teeth should not be removed without due consideration, for they cannot be replaced and are necessary to the general well-being of the patient. Skilful tonsillectomy entails fewer far-reaching disturbances. In the elimination of infections which may be a possible cause of arthritis and rheumatism, it is essential to realize that mere removal of infection will not necessarily restore the patient to health, because after long-continued intoxication the physiology is more or less permanently dislocated, and because the lymph-glands may retain infection sufficient to perpetuate the active pathological processes. The manifold sequellæ may also prolong or prevent permanent cure, unless they are properly treated. For this reason after the foci of infection have been removed in so far as possible, the general bodily resistance should be raised.

In certain cases arthritis is apparently not caused by focal infection in the usual sense, but is in some way due to conditions in the intestinal tract, particularly in the colon. Consequently, treatment should prevent or retard the absorption of any toxins which may be formed in the alimentary canal and favor elimination of the intestinal contents. Lavage of the colon, or even catharsis, as well as abdominal and colonic massage, are of definite but limited value. The danger incurred in such operations as ileocolostomy or colectomy detracts greatly from their usefulness, but in certain cases they have proved a successful form of treatment. Restriction of diet is also desirable in that it may prevent the formation in the intestines of abnormal end-products of digestion, and, furthermore, permit nutrition without placing an undue load upon the tissues of the body.

To decide just when the diet should be limited is difficult. Although restriction probably produces a certain degree of subjective improvement in about 50 per cent. of all patients, no matter what the etiology, it cannot be of fundamental help except under conditions of adequate nutrition. The diet should, therefore, be curtailed only when no foci of infection can be found or when the removal of infection and other forms of treatment have proved ineffective. Anemia or emaciation may constitute limitations or contra-indications to restrictions of diet. The curtailment of the food intake usually requires a readjustment of habits in order to prevent too great expenditure of energy and to avoid exhaustion and asthenia, for it is probably the quantity of food as well as the type which produces the harmful effects. This has not been fully recognized in the past.

It is probable that neither the carbohydrates, fats, nor proteins exercise a specific influence upon the pathological processes of arthritis. Of the three foodstuffs, carbohydrates constitute the largest part of any normal diet and are most easily burned. For this reason they are probably more

harmful than either the proteins or fats. Nearly 60 per cent. of the protein ingested is, however, converted into carbohydrate within the body. When it is necessary to limit the diet in the treatment of arthritis, the caloric intake should at first be reduced to about 30 calories per kilogram of body weight. This may be derived from all three types of food; but the proportion of carbohydrate should be somewhat smaller and that of fat somewhat larger than normal. Bulky food, such as salad, apples, celery, beets, etc., gives patients more satisfaction than concentrated food, because it makes meals appear more ample. Since definite rules cannot be given for the exact apportionment and choice of foods, the following example of a suitable restricted diet for a man of about 70 kgm. or 154 pounds is included:

		Calories.
BREAKFAST		
1 apple	150 gm.	72
1 egg	50 gm.	83
Bread	60 gm.	162
Butter	15 gm.	120
Sugar	20 gm.	80
Milk	60 c.c.	39
Coffee		
LUNCH		
Bouillon	180 c.c.	
Lettuce	40 gm.	
Mayonnaise	1 tablespoon	187
String-beans	100 gm.	17
Bread	30 gm.	80
Butter	10 gm.	80
Orange	250 gm.	96
1 egg	50 gm.	83
SUPPER		
Steak	50 gm.	143
Bread	60 gm.	160
Butter	15 gm.	120
Tea		
Sugar	20 gm.	80
Milk	60 c.c.	39
Beets	100 gm.	40
Lettuce	40 gm.	
French dressing	2 tablespoons	298
1 apple	150 gm.	72
Total calories		2051

The use of such a diet may in some cases reduce the inflammation in the small joints, the fingers for instance, within two or three days, while in others its effects may not be manifested for weeks or months. In the so-called proliferative type of arthritis, dietetics play an important rôle in treatment, especially in well-nourished persons, and the caloric intake may then be reduced with less risk than when the case is complicated by malnutrition. The use of dietary methods in the treatment of Still's disease demands caution and the constant consideration of the nutritive necessities of the growing child. Increasing quantities of cod-liver oil may be added slowly to the restricted diet in order to prevent undernourishment and improve the general condition of the patient, but only when careful watch is kept for the return of arthritic symptoms.

Improvement of the General Condition.—In addition to the removal of the known and suspected causes of the pathological processes of

arthritis, certain measures which raise the general resistance and improve the physical condition of patients should be employed. The rules of hygiene should be scrupulously followed, and the patient should be out of doors as much as possible. *Specific vaccines* and *non-specific proteins* may be injected. If they do not prove beneficial they are at least harmless unless they produce undue reaction. Autogenous vaccines are preferable to those commercially prepared, but either may be administered. Injection of standardized typhoid vaccine intravenously in doses of 10,000,000 to 15,000,000 or more is helpful in the treatment of acute and subacute cases, but only when the patient is sufficiently strong to withstand the ensuing reactions. Chronic cases derive but doubtful benefit from such treatment. Experience has demonstrated that the larger doses advocated a few years ago must be employed with great caution. Other forms of non-specific proteins have also acquired some vogue, such as milk, in purified form, and streptococci in the form of Coley's fluid. These have the advantage that they can be given subcutaneously, but the local and general reaction may nevertheless be severe. The results are sometimes very gratifying, especially in relief of pain, but the dosage must be small at the outset and slowly increased.

The general condition of the patient may also be greatly improved by stimulation of the metabolic processes. *Radium emanation*, when properly administered, is a very valuable metabolic whip. Since, unfortunately, many of the commerical preparations to which value is ascribed contain but little or no emanation, this agent should only be employed by those who thoroughly understand and can control it. *Thyroid extract* is also beneficial, but cannot be depended upon in all cases. It is dangerous in that it may produce hyperthyroidism. In the treatment of the exhaustion so characteristic of arthritis *arsenic* plays a rôle of great and permanent importance. It increases the general metabolism, produces a gain in body weight by improving the appetite, and in large part abates the painful processes. When administered to patients with chronic arthritis which is accompanied by secondary anemia it causes a very marked general improvement while the blood is being restored to normal. This effect may be permanent. Arsenic should be administered in small doses, since the limit of tolerance may be quickly and suddenly reached. To the initial dose of 1 minim of Fowler's solution three times a day, 1 minim once a day may be added. Instead of Fowler's solution, $\frac{1}{4}$ grain of sodium cacodylate may be administered hypodermically once a day with 1 grain of ferric citrate. The time-honored use of the iodids in the treatment of rheumatic infections may possibly also depend upon their influence on metabolism. In subacute and border-line cases they may produce great improvement. If they are not helpful, they are at least harmless.

But it is not by drugs alone that the metabolism is stimulated. One of the oldest forms of treatment is the *external application of heat*. This causes a general systemic reaction when applied to the body as a whole, and a local reaction when applied to the diseased regions. The general reaction is evidenced by an increase in the pulse rate and in the circulation, by profuse sweating, by hyperpnea, and by unusual elimination of CO_2 from the lungs. The loss of the acid radical leaves in the blood an excess of alkali which is excreted in the urine and perspiration and renders them alkaline. Such changes may be very beneficial in the treatment of arthritis, but

must be maintained and repeated for long periods if their effects are to be permanent. Local application of heat must also be continued at intervals for a long time if the ensuing improvement in local circulation and metabolism is to accomplish lasting benefit. Hydrotherapy, which consists essentially in the application of heat, is a form of treatment which may be very beneficial or it may produce exhaustion and even permanent harm if incorrectly used. Frequently, the application of heat both generally and locally is advisable.

Massage, which also has long been advocated for the treatment of arthritic conditions, is another form of therapy which may easily be misapplied. When general it may be of great help to sedentary patients if it is not too violent. The value of local massage is in the production of hyperemia around the diseased joint; and its danger, in the addition of trauma to the existing inflammation when the joint is moved or massaged too vigorously. In atrophied muscles it not only promotes development of muscle tissue, but also favors the normal metabolism of the muscular system, which is essential to physical well-being. When applied to arthritic joints massage should never be so severe as to increase discomfort if the pathological processes are active; when the diseased condition is chronic, however, the vigor of manipulation and movement may be increased very gradually to permit stretching of the ligaments and tendons, but with great care to prevent further injury. When applied to wide-spread rheumatic myositis, massage may sometimes act almost like a specific. Exercise, which is still another means of stimulating metabolism, must, too, be prescribed with due caution. Although electricity has been widely employed in the treatment of arthritic conditions, its action is not definitely understood. It produces effects similar to those of these other forms of external treatment. Diathermy may be very beneficial to the patient, and the galvanic current may also play a limited but useful therapeutic rôle.

To improve the general health of patients more or less crippled by arthritis, *orthopedic measures* are sometimes necessary. Correction of local deformities, or suitable adjustment to them, may minimize a tendency toward general deformity and permit more normal activity of the visceral and thoracic organs. Patients who are chair- or bed-ridden tend to assume a slouched position in which the limbs are flexed, the shoulders rounded, and the thoracic and abdominal contents crowded together as in kyphosis. This may be avoided if the patient lies flat in bed for a large proportion of the time, or even hyperextended with a small pillow at the level of the fourth or fifth thoracic vertebra. Exercises in thoracic and diaphragmatic breathing not only favor aëration of the blood and improve the chest expansion, but also exercise the abdominal muscles, which tend to become flabby, and agitate the abdominal organs. Although marked enteroptosis can be cured only by strengthening the muscles and increasing the quantity of intra-abdominal fat, abdominal supports and anterior-posterior pads sometimes help the patient to regain and hold a correct posture.

As *damp* and *sultry weather* appears to aggravate rheumatic infections, and even to precipitate them, many places and climates have been recommended as favorable to the cure of such disturbances. Experience seems to show that comparative dryness, ample sunshine, and moderate altitude are of great benefit but only when the condition of the patient favors convalescence.

Specific Treatment.—Of the various drugs advocated to allay the pain of arthritis only a few have stood the test of time. The *salicylates* are the most important of these. That they lessen the discomfort, even in advanced cases, is well known, but whether they shorten the duration of acute or subacute arthritis is questioned. Probably they do cause subsidence of the painful processes of the acute form of the disease if they are administered at the onset. As continued use of these drugs sets up digestive disturbances, it should always be borne in mind that they produce the best and most permanent effect when administered in relatively large doses for a short period of time. Salicylic acid is most frequently given in the form of sodium salicylate. The dose may be as large as 20 grains three or four times a day, and should be accompanied by an equal quantity of sodium bicarbonate to prevent acidosis. The modifications of salicylic acid, and the substitutes, such as aspirin, tolysin, and cincophen, may be administered in somewhat smaller quantities. They are less likely to disturb the digestion.

Although neuritis and neuralgia are but local manifestations of a general systemic condition which must be remedied, they may be treated locally as well as indirectly. The salicylates are useful for this, and also locally applied heat, skilful massage, counter-irritation, and even Paquelin cauterization.

After joints or limbs have become diseased, orthopedic treatment often prevents permanent or increasing deformity. The knees may be straightened, the back braced, and flat-foot and deformities of the toes corrected by measures quite foreign to the practice of internal medicine. The orthopedist may also detect conditions like sacro-iliac subluxation which might baffle the general practitioner. The use of splints sometimes prevents or corrects such deformities as subluxation and foot-drop.

Experience has demonstrated that when a single therapeutic measure proves unsuccessful or comparatively ineffective, it may be rendered very helpful by combination with other forms of treatment. This was particularly noticeable in dealing with the arthritis which attacked large numbers of soldiers in the United States Forces during the War. When, for instance, stimulation of the metabolism is beneficial, measures which reduce the metabolic "load" of the tissues may still further increase its effectiveness, but such combined treatment demands close and constant observation of the patient. Certain types of treatment, however, cannot be combined without incurring danger. Stimulation of the metabolism by the administration of non-specific protein, massage, or hydrotherapy is usually undesirable if the patient is asthenic or living on a very low ration, because it may entail depletion of the reserves within the body.

Success in the treatment of chronic arthritis depends not only on the suitable employment of the various measures mentioned, but also on the co-operation of the patient and attention to many details. Without a proper point of view and reasonable encouragement, patients are liable to lose their morale and refuse to follow the prescribed routine intelligently and faithfully. Improvement depends as much upon continued adherence to the necessary régime as upon the type of régime. At times it is necessary to exercise the strictest discipline in dealing with patients and to control everything within their horizon.

Ralph Pemberton.

ARTHRITIS OF THE MENOPAUSE

Definition.—A chronic polyarthritis of obese middle-aged women occurring at or just after the menopause.

Etiology.—In a series of 50 cases studied by Cecil and Archer the average age was fifty-two and a half years. All races are susceptible. In most cases the patient is considerably overweight. The symptoms usually appear during the first two years after the menopause. Sometimes the arthritis occurs simultaneously with the menopause and in a few cases the rheumatic symptoms precede the change of life by a short interval. The disease does not appear to be of infectious origin.

Morbid Anatomy.—The condition affects chiefly the end of the bone and the articular cartilage. The latter becomes thin and eburnated and there is lipping of the bone at the margin of the joint, with often an actual increase in the area of the articular surface. In the great majority of cases there are no periarticular changes.

Symptoms.—The disease develops insidiously. The first symptom, as a rule, is a slight stiffness in the knees. Gradually this becomes more noticeable especially in walking or bending the knees.

In the series studied by Cecil and Archer the knees were the first joints affected in 84 per cent. of the cases. The lumbar vertebræ and the bones of the feet are often involved. In a large percentage of patients there are well-developed Heberden's nodes on the distal interphalangeal joints. Occasionally a shoulder- or hip-joint may become implicated.

Physical examination yields very little. The patient is overweight and the posture is usually bad. Pes planus is common. Examination of the joints involved shows little if any swelling. On flexion a certain amount of crepitation is usually detected. Radiographs of the joint show distinct lipping and spur formation. True ankylosis does not occur.

The course of the disease is very slow, and there is little tendency toward involvement of other joints. On the other hand, spontaneous recovery seldom, if ever, occurs.

Treatment.—The most important part of the treatment is reduction of the patient's weight, which is best accomplished by a low calory diet consisting chiefly of green vegetables. Iodids and thyroid extract are also of value. Physiotherapy, especially diathermy, gives much relief. Some patients are much benefited by colonic irrigations. Vaccines are of little value.

Russell L. Cecil.

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Diseases of the Bones

OSTEITIS DEFORMANS

(*Paget's Disease*)

Definition.—Osteitis deformans is a chronic disease of the skeleton which appears in middle life or later, and is characterized by extensive hypertrophy

and bowing of the long bones and enlargement with irregular deformation of the flat bones. The disease was first accurately described by Paget in 1877. It is one of the most common of the bone diseases.

Incidence.—The disease seldom begins in individuals over fifty or under thirty years of age, the average at onset of 48 patients being forty-five and a half years. Males are more susceptible than females. There is undoubtedly an hereditary tendency (29 per cent. of the series of 48 cases).

Etiology.—The cause of the disease is unknown. Gout, rheumatism, syphilis, bacterial infection, trauma, malignant disease, disorders of the endocrine glands and trophic nerves, and arteriosclerosis are commonly mentioned as possible factors concerned with the etiology. With the exception of the last mentioned, however, there is no convincing evidence of such a relationship. General and extreme atheroma of the arteries is almost invariably present and strongly suggests that this process plays some etiological rôle.

Morbid Anatomy.—Any part of the osseous system may be attacked, but the process is primarily concerned with the skull and long bones. Its starting-point seems to be in the tibiæ and skull. In the late stages of the disease radiographs may show a generalized involvement of practically the entire skeleton. The changes are usually irregularly bilateral. In all affected bones there is a general thickening, and in the axial bones a bowing as well. Ultimately, the entire shaft and even the epiphyses are involved. The slight longitudinal growth which finally takes place is probably the chief cause of the bowing. The surface of the bones becomes very uneven and the general contour fairly irregular. The bowing is broad and even throughout the entire length of the bone. Osteophytes are rare. Normal markings, which at first may be hypertrophied, are later entirely lost. The periosteum is hyperemic and moderately adherent. On section the bone presents a very varied appearance; for the most part it is irregular and spongy with marked evidence of increase of the blood-supply, though in many places its texture is like ivory. An increase in the fat is very evident in both the marrow and spongiosa. The marrow spaces may finally become entirely obliterated. Cysts are rare and always small. The changes consist of wide-spread rarefaction (malacia) and formation of new bone, essentially of connective-tissue origin. Subperiosteal proliferation also occurs. Spontaneous fractures and localized periostitis are common.

The skull is always involved, usually in the early stages, the lesions being largely confined to the calvarium which becomes enormously thickened and enlarged.

The joints are not primarily affected. A general and exceptionally marked degree of arterial atheroma is the rule.

Chemical changes in the bones are somewhat variable. The quantity of organic matter, especially of the fat, is much increased while the amount of lime is decreased, often as much as 50 per cent. The magnesium content is also reduced, while the chlorin, phosphorus, and sulphur contents remain normal. Metabolism experiments have given inconstant results, but in general there is a considerable retention of calcium, magnesium, and phosphorus, and a loss of sulphur.

Symptoms.—The onset of osteitis deformans is so insidious that the patient seldom comes under observation until the disease is far advanced,

the gradually increasing disability and deformity being attributed to old age. The symptoms are largely objective and concerned with the deformities. Beginning in a single bone, usually the skull or tibia, the disease gradually invades much of the rest of the skeleton; but a rare "mono-osteitic" form in which the lesions seem to be confined to a single bone has been described by Schlesinger and Hurwitz. In well-developed cases the general picture is very striking. The whole calvarium is much enlarged, the head is carried forward with the chin almost resting on the chest, and the movements of the head are greatly restricted. The spine is bent markedly forward and is rigid; the bones of the shoulder girdle are massive; the thorax is compressed laterally; the pelvis is very broad and massive; the legs are bowed forward and outward. The arms may likewise be bowed, the upper arm forward and the forearm outward and forward. A marked flexion of the trunk on the legs compensates for their bowing and permits maintenance of equilibrium. As a result of the deformities there is a marked reduction in stature, often as much as 6 inches. On standing the feet are strongly everted, with one a considerable distance in front of the other. The gait is labored and waddling.

Pain is the most prominent and usually earliest subjective symptom. It may be of all grades and varies in character from a dull soreness to the most intense paroxysmal type. It is worse at night and after long standing or walking. The most common site is along the shins where it is apt to be associated with localized periostitis. Pressure over the affected bones often produces exquisite pain. Intense cramps in the lower legs are almost constantly observed. Muscle atrophy ultimately develops. Fractures of a spontaneous type, or following some trifling trauma, are of frequent occurrence. Fatigue, general weakness, cardiovascular symptoms, impairment of sight and hearing follow. The sensations, reflexes, blood, and excretions are normal. Among the complications, malignant disease of the bones, cardiovascular disease, apoplexy, emphysema, bronchitis, and pulmonary tuberculosis are the commonest.

The characteristic radiographic findings in the well-developed stage are as follows: the long bones are enlarged throughout with a broad bowing from end to end. The outlines are relatively even except for the variations in the deposits of lime-salts just beneath the periosteum. No medullary canal is shown and but little evidence of periosteal formation of new bone. The structure of the osseous tissue is entirely altered and appears to be feathery or mossy throughout the shaft with a coarse trabeculation near the joint ends. Areas of very dense bone are often present and small cysts are occasionally seen. The whole picture is that of a combined process of rarefaction and ossification.

The *course of the disease* is particularly chronic; the gradually increasing deformities finally lead to more or less complete crippling. Its total duration is frequently twenty or thirty years and the majority of patients live to old age. Occasionally the disease becomes quiescent, and allows the victim to live on for many years without perceptible increase in the deformities. Death is never the direct result of the osteitis, although in a few cases it has seemed to be caused by a fatal cachexia. Most commonly it is due to cardiovascular or malignant disease, pneumonia, pulmonary tuberculosis, or apoplexy.

Diagnosis.—Even in its early stages Paget's disease is readily differen-

tiated from other affections of the skeleton by its special and grotesque characteristics.

Acromegaly typically attacks for the most part the soft tissues, only the small bones of the hands and feet being affected. The face becomes gross and of a characteristic oval shape in contrast to that of osteitis deformans which is triangular. The calvarium and long bones are not changed. Pain, which is a prominent and fairly constant symptom of osteitis, is absent in acromegaly.

Osteoporosis senilis is a condition seen in the aged, which characteristically causes atrophy and an increase in the fragility of the bones without striking deformity.

Bow-legs in adults may be the result of rickets in childhood, and should never be confused with osteitis deformans.

Osteomalacia occurs almost exclusively in women during the third and fourth decade. The changes in the pelvis are much more pronounced than those of osteitis. The skull is only slightly affected, if at all. Deformities in the long bones are angular and irregular in contrast to the broad bowing of osteitis. Atrophy is the predominating feature in the bones during osteomalacia, while proliferation is the chief characteristic in Paget's disease. The *x*-ray clearly differentiates the two processes.

The osseous changes in the individual bones affected by *ostitis fibrosa cystica* may closely resemble those of osteitis deformans. In the former, however, fibrous metaplasia, cysts, and tumors are much more prominent features and fractures more frequent. The process furthermore is apt to to be confined to the proximal portion of a single long bone. The outward deformities of the bones are angular bending and irregular localized enlargement due to the formation of tumors. No involvement of the skull occurs.

Localized hyperostosis due to lues, especially of the tibia, may occasionally suggest osteitis deformans. The lesion, however, is confined to a portion of the shaft only, and consists of a more or less spindle-shaped, dense enlargement. The remainder of the skeleton remains unchanged. The Wassermann test and *x*-ray examination are of great diagnostic assistance in doubtful cases.

Treatment.—Little can be said in favor of any specific form of therapy. Osteotomy for the correction of deformities has been strongly advocated by some and practiced in a few instances, but the very meager results do not seem to justify the procedure. Orthopedic measures designed to accomplish the same end have proved useless. Analgesia and local counter-irritation often relieve the troublesome pain. Tonics may be useful.

Edwin A. Locke.

OSTEITIS FIBROSA CYSTICA

(von Recklinghausen's Disease)

Definition.— Osteitis fibrosa cystica is a chronic progressive disease of the skeleton which usually begins in late childhood and is characterized by

a gradual metaplasia of the normal bone into fibrous tissue. Multiple, non-malignant, giant-celled tumors, and cysts are usually present. In the common or localized form the lesions are confined to a single bone, while in the generalized form many bones are often involved. Less than 100 cases of this disease have been reported.

Incidence.—It is usually stated that the disease almost invariably develops between the tenth and twentieth year, but recent observations suggest that the process frequently begins much earlier. Females are somewhat more commonly affected than males. We know nothing of the actual course of the disease. The majority of recent investigators regard the condition as a dystrophy of developing bone combined with chronic inflammation.

Morbid Anatomy.—The long bones are most often involved (humerus, tibia, and femur), but in the generalized form any or every bone except the skull may be affected.

The principle anatomical changes are a diffuse halisteresis combined with degeneration, the development of fibrous tissue, the formation of benign giant-cell tumors and cysts, bowing, and fractures. The proximal part of the long bones which is primarily the seat of the disease becomes enlarged.

Microscopically the diseased portion of the bone presents a most complex and confused picture. A high degree of absorption of lacunæ and various stages of fibrous metaplasia are general throughout the bone and marrow. The cortex in many places is reduced to a mere shell. The periosteum is inactive. Hemorrhage plays an important part in the picture. Small or large fibrous tumors are seen and single or multiple cysts filled with brownish or whitish, gelatinous, or serous fluid. The epiphyses undergo but slight change. Fractures are seldom absent and may be multiple. Callus formation is active and healing fairly prompt. Because of the changes described the bone becomes extraordinarily flexible.

Symptoms are not prominent and appear only when the disease is well established. A fracture from some trifling injury is very frequently the first manifestation of the disease. It is most apt to occur in the humerus or femur. Pain is often an early symptom, but never very prominent. There may be tenderness over the diseased portion of the bone.

With the appearance of the deformities marked disability develops. Complications do not occur. The course is chronic and varies from months to many years.

x-Ray examination is of the utmost importance, as not infrequently it is the only means of determining the true nature of the process. It shows that the outline of the bone is fairly regular, the periosteum intact, and the epiphyses seldom altered. On the other hand, the diaphysis shows almost no normal markings. The outstanding evidences of the disease are the general and marked atrophy with the formation of cysts.

Diagnosis is often difficult, largely because of the considerable number of other conditions in which osseous cysts may develop. The differentiation between this disease and *osteitis deformans* and *osteomalacia* has been discussed with these diseases.

In *malignant tumors* of the bone the local symptoms are much more prominent and the general symptoms severe. Metastases sooner or later develop. The process is at first localized in a single bone. The *x*-ray fails to show the changes typical of ostitis fibrosa.

Tuberculosis of the bone is a disease of the epiphysis which presents al-

most none of the characteristics of ostitis fibrosa. The *x*-ray, furthermore, gives a distinctive picture in the two conditions.

Syphilis is to be differentiated by the absence of the clinical picture of ostitis fibrosa, the *x*-ray findings, and the Wassermann test.

Treatment.—Excellent results have been thought to follow a variety of surgical procedures, namely, aspiration, curettage, osteotomy, and excision. The generally accepted method of surgical treatment is to lay open the cyst and curet out the shell of diseased bone. Fractures require the same treatment as ordinary fractures. Mobilization of the affected extremity is occasionally necessary to protect the diseased bone from injury and fracture.

General hygienic and dietetic measures should be carefully carried out. Calcium lactate has been strongly recommended and should be administered.

Edwin A. Locke.

LEONTIASIS OSSEA

(General Hyperostosis of the Skull, Megalocephaly)

Leontiasis ossea is a rare disease, which was first described by Malpighi in 1697, but did not receive the name of *Leontiasis ossea* until Virchow published a more complete description in 1864. The chief feature of the disease is a diffuse, and ultimately an enormous hyperostosis, of all the bones of the skull and especially of the lower jaw. The enlargement is in general symmetrical, and leaves the surface of the bone rough but free from large exostoses. In very rare cases the process may invade other parts of the skeleton as well. The hyperostosis is so extreme that the skull in some of the museum specimens weighs more than 4000 gm. (2 pounds), and the thickness of the calvarium is 2 inches or more.

There is both an eccentric and concentric overgrowth of bone with a resulting encroachment on all the cavities and foramina of the skull, which leads to pressure on the brain. All bony canals for the passage of nerves and blood-vessels are narrowed. The orbits in particular are more or less filled in and the sinuses are sometimes entirely obliterated. For the most part the bone is increased in density and often becomes as hard as ivory, although in certain areas it is abnormally porous.

The **symptoms** of the disease are entirely subjective and the direct result of pressure. *Headache* of a very severe and persistent type is often an early symptom. *Exophthalmos* is nearly always present. Blindness, deafness, neuralgia, paralysis, and extreme dilatation of the veins follow. Finally insomnia, mental dulness, weakness, convulsions, and even insanity may appear.

The disease is seen more often in females and develops at the time of puberty or a little later. The cause is not known, although trauma in some cases has seemed to be of some etiological significance.

The course of leontiasis ossea is usually from twenty to forty years;

frequently the disease becomes quiescent. Death often results from inanition, but may occasionally occur suddenly with a convulsion.

Diagnosis, except in the early stages, is never difficult. In *acromegaly* the changes in the extremities are distinctive, while those in the face are of an entirely different type. *Paget's disease* bears no real resemblance to leontiasis ossea, and is seen much later in life. The general type of deformity, the more general involvement of the skeleton, the gait, and absence of more than very slight changes in the bones of the face serve to distinguish it from leontiasis ossea.

Treatment is restricted to surgical procedures to relieve pressure.

Edwin A. Locke.

HEREDITARY DEFORMING CHONDRODYSPLASIA

(*Multiple Cartilaginous Exostoses*)

Definition.—Hereditary deforming chondrodysplasia, which is hereditary and congenital, is characterized by multiple cartilaginous and osteocartilaginous proliferation of the metaphysis of the long bones. The arrested development in the affected bones leads to secondary deformities. Ehrenfried has collected 600 published cases.

Incidence.—The disease is more common in males than females, the ratio being 3 to 1, and probably even greater. As the disease is congenital the bone changes begin at an early age, but, since the chief clinical manifestations are those of deformities, they become evident only with the growth of the bones and are, therefore, seldom recognized before the fourth or sixth year. A familial occurrence is very common, transmission usually taking place directly through the male. The cause is probably a defective development (proliferation and ossification) of the intermediary cartilage, *i. e.*, a chondrodysplasia.

Morbid Anatomy and Symptoms.—The essential characteristics of the disease are (1) exostoses, and (2) retardation of skeletal growth, both types of lesions showing an irregular symmetry. The *exostoses* are extremely irregular, cauliflower-like proliferations at the diaphysial ends of the long bones, and vary in size from very small spurs to formations as large as a hen's egg. There may be a hundred or more tumors. True enchondromata are sometimes seen. The *deformities* due to *retarded development* are much less conspicuous, but are invariably present. They consist primarily in underdevelopment of the metaphyseal portion of the long bones (femur, tibia, fibula, ulna, and radius). A slight to moderate degree of dwarfism results, but never of the striking type seen in achondroplasia. The central point of the body is only 1 or 2 inches above the symphysis. Joint function is often mechanically limited, and the articulations may be distorted.

While the objective signs are striking, primary symptoms are entirely lacking, and such as do occasionally occur are due to complications or to secondary changes, as, for instance, in the joints. The development of malignant osteochondromata, fracture, erosion of a blood-vessel with re-

sulting aneurysm, pressure on nerve-trunks causing neuralgia or paralysis, and signs of compression in the cord have been recorded.

Roentgenographic examination shows the bony deformities described above. Their density and structure are extremely varied. The shaft of the affected bone is occasionally increased in density, but more often shows a decreased density with a longitudinal pencilling.

The **prognosis** is excellent, as the general health is unimpaired and the rare complications seldom affect the length of life. Growth of the exostoses eventually ceases and the deformities become fixed at the time of skeletal maturity. Patients have been observed to have definite retrogression in the tumors at this period.

Diagnosis.—Apart from the superficial resemblance to mild cases of *achondroplasia*, a typical case can hardly be confused with any other disease. The multiple exostoses seen in this disease are unique, as are the *x*-ray pictures.

Treatment.—Mechanical or surgical treatment often gives relief from symptoms caused by pressure.

Edwin A. Locke.

SECONDARY HYPERTROPHIC OSTEO-ARTHROPATHY

(*Hippocratic Fingers, Ostéo-arthropathie Hypertrophiante Pneumique, Marie's Disease*)

Definition.—Secondary hypertrophic osteo-arthropathy is a general and symmetrical hypertrophy of the distal phalanges of the fingers and toes with resulting clubbing, frequently accompanied by enlargement of some of the other bones of the hands and feet or by hypertrophy of the bones of the forearms and lower legs. These changes are associated with a considerable variety of diseases, chiefly chronic affections of the heart and lungs.

History.—Among the early medical writers Hippocrates particularly described clubbed fingers as developing in the course of chronic phthisis and empyema. In 1889 Bamberger gave the first account of the "ossifying periostitis" in the bones of the forearms and legs accompanying clubbing of the fingers in 2 cases of bronchiectasis. Marie, in the following year, published his careful studies of 8 cases of this disease, which he called "ostéo-arthropathie hypertrophiante pneumique."

Etiology.—The condition is probably always secondary, although the literature contains reports of 6 typical cases with no evidence of any antecedent disease. In 1915, Locke was able to collect 144 published cases, of which 112 followed primary disease of the respiratory tract, 6, diseases of the circulatory tract, 13, diseases of the alimentary tract, and 13, unknown or miscellaneous disturbances. The list of primary diseases is surprisingly large, but the majority of cases occur with bronchiectasis, pulmonary tuberculosis, empyema, malignant disease of the lung and mediastinum, valvular and congenital heart affections, biliary cirrhosis, congenital syphilis, and chronic enteritis. Osteo-arthropathy unquestionably appears most frequently in association with pulmonary tuberculosis.

The real cause of the changes seen in this disease has not yet been proved.

The original theory of Bamberger and Marie that the lesions are the result of toxic absorption, *i. e.*, a chemical action, finds strong support in the fact that the vast majority of cases are secondary to some bacterial disease. On the other hand, this hypothesis fails to explain the occurrence of osteoarthropathy after such affections as congenital heart disease when there is no suppuration. It is known, however, that chronic venous stasis may induce proliferation of bone, and it has been suggested that such mechanical effects on the circulation may lead to the same changes in the distal parts of the extremities as does toxemia. For the present we must admit the possibility of the action of two factors, a toxemia, bacterial or otherwise, and chronic passive congestion acting either alone or combined, as the cause of the disease.

The disease is more common before middle life. Landis found that it occurred 8 times more often in males than in females.

Morbid Anatomy.—The outward deformities and histological changes in the bones invariably conform to a fixed type. The most striking feature of the disease is the bulbous enlargement of the terminal phalanges of the fingers and toes, which is largely due to changes in the soft parts. The nail becomes thickened and curved in both directions, sometimes so markedly as to resemble a parrot's beak. Longitudinal ridges of the nails are common. About the nail-bed the tissue is puffed, smooth, reddened, and the nail is felt to float. These conditions are probably due less to edema than to proliferation of the connective and fatty tissue and to injection of the capillaries. The end of the entire finger, and especially the region under the nail, is apt to be cyanotic. In some of the most marked cases the entire hand is enlarged until it assumes a puffy, paw-like appearance. In a fair percentage of cases the ungual phalanx shows a general proliferation when examined with the *x*-ray.

In the most severe cases there are, besides the enlargement of the terminal phalanges, significant lesions of the bones of the forearms and lower legs, of the tarsus and carpus, rarely also of the femur, and humerus. Even the flat bones of the skeleton may be slightly involved. General rigidity and kyphosis occasionally develop in the late stages of the disease. The process always begins in the distal third of the diaphysis of these bones, though with the advance of the disease the entire shaft becomes involved. The alterations consist primarily in the formation of a very irregular layer of new bone just under the periosteum. *x*-Rays reveal this as a shell surrounding the old shaft. In the early stages, it is plainly differentiated from the original bone by reason of the fact that it is poor in lime salts, but later it becomes very dense and so closely united to the original bone that the line of demarkation between the two is entirely lost. The process is a true progressive ossifying periostitis. Late in the disease the entire bone may undergo a rarefying inflammation similar to that so characteristic of osteitis deformans. Bowing never takes place, but an actual lengthening of the bone does rarely occur. The epiphysis which is at first unaffected, later becomes invaded with a very irregular, moss-like layer of new bone. Cysts are rare. Suppuration never occurs.

Together with the osseous changes a very considerable thickening of the surrounding soft tissues takes place and gives to the distal half of the forearm and lower leg a clumsy, cylindrical appearance. Muscular atrophy finally develops.

The joints (wrists, knees, ankles, elbows, and small joints of the hands and feet) are involved only late in the course of the most severe cases. A low-grade synovitis with hydrops and erosion of the interarticular cartilage is the usual condition found. Actual ankylosis is rare, and dislocations are unknown.

Symptoms.—The onset is insidious. In the simplest form, namely, when the disease is confined to the terminal phalanges, there are no symptoms. On the other hand, when the long bones are involved, symptoms become more and more prominent. Pain is almost constant, and varies from mild discomfort to a most distressing, deep-seated ache over the forearms and lower legs. It is often intermittent, occurring only at night or after long standing. The pain is invariably accompanied by sensitiveness over the affected bones. When the disease is well advanced the joints very often become stiff and painful, but signs of actual inflammation have only been observed in rare instances. A rise in temperature is said to accompany the joint symptoms, and inflammation of the lymph-nodes in the groins and axillæ has been observed.

In the late stages of osteo-arthropathy general emaciation, weakness, and anemia become very marked. Kyphosis may supervene and finally render the patient almost helpless. Among the rarer symptoms a variety of skin lesions have been described—ichthyosis, eczema, erythema, and pigmentation. Profuse sweating may be an annoying symptom.

The clinical course is extremely variable, but in a general way follows that of the primary disease. Any marked change in the latter is apt to be reflected in the former. Exacerbations and remissions are for this reason common. The writer has seen 2 cases of this type. There was a very abrupt onset with violent pain, sensitiveness, high fever, and great prostration. After a few weeks the symptoms gradually subsided. Not only may the symptoms and the objective signs subside, but an actual absorption of the new bone gradually takes place as proved by *x*-ray examination. As a rule, the onset of the disease is very gradual and insidious and its course very protracted, but occasionally well-marked clubbing may develop in one or two weeks as with empyema. The duration often covers a period of many years.

Diagnosis.—The distinctive features in this disease usually leave no uncertainty in diagnosis. In the late stages the large, paw-like condition of the hands may suggest acromegaly, but in no other respect is there even a superficial resemblance.

Treatment.—The therapy of osteo-arthropathy is essentially the treatment of the primary disease. Symptomatic treatment of pain and of the affected joints often gives great relief.

Edwin A. Locke.

OSTEOMALACIA

Definition.—Osteomalacia is a disease primarily of adult females, which usually runs a progressive chronic course with the essential lesions confined to the skeleton. The process consists of a combination of wide-spread

softening and absorption of old bone with the formation of new and uncalcified osseous tissue.

Four varieties are described: puerperal, non-puerperal, juvenile, and senile. To this group of clinical forms should perhaps be added a fifth, *i. e.*, the so-called "*hunger osteomalacia*," which has been seen with ordinary frequency in Austria and certain parts of Germany since the Great War. These cases have shown wide-spread softening of the bone as well as striking clinical features which seem identical with those of true osteomalacia. Individuals thus affected have come almost exclusively from the destitute classes who have suffered severely from bad hygiene and insufficient food. It cannot be doubted that the disease is dependent on nutritional disturbances, but whether due to the deficiency of fat, albumin, lime, or phosphorus it is impossible to say. Its association with pregnancy has not been particularly evident. In a considerable percentage of cases the administration of a full normal diet is followed immediately by marked improvement or, ultimately, by complete recovery.

Osteomalacia is a relatively common disease among all domestic animals, but only among those who lead a stall life. Its prevalence varies greatly with different localities. The theory that in animals it is due to a deficiency of lime in the food has received very substantial support from the results of experimental studies.

Incidence.—A great majority of cases occur between the ages of twenty and thirty. The disease is very rare at the extremes of life. Females are said to comprise about nine-tenths of the number of patients, and probably at least two-thirds of the cases are associated with pregnancy and lactation. Osteomalacia is almost wholly confined to those who have numerous and frequent pregnancies. Heredity plays no part. The disease bears some relation to poor general hygiene and undernutrition, although it rarely attacks the well-to-do when neither factor is present. In children especially osteomalacia often follows an infectious disease. Certain cases strongly suggest a dependence on dysfunction of the glands of internal secretion, especially the thyroid, adrenals, and ovaries. Osteomalacia is found very widely distributed over all parts of the world, but is very prevalent in certain localities, particularly in central Europe. None of these factors, however, offer any real explanation of the cause of the disease.

Etiology.—McCrudden's metabolism studies in osteomalacia show a marked and constant increase in the excretion of calcium with a retention of sulphur and magnesium. Such results are in keeping with the known composition of the diseased bones, *i. e.*, a deficiency in lime, but an abundance of organic matter. Normally during pregnancy there is apt to be a slightly diminished calcium content in the bones—"physiological osteomalacia." It is the general belief that in the development of the fetal skeleton the chief source of the lime is the maternal bones. Under normal conditions the lime deficiency during pregnancy is soon made up, but in the case of rapid pregnancies the drain on the mother's bones may be so great as to prevent the maintenance of a normal calcium balance and osteomalacia results (McCrudden). On the basis of this theory it is not unreasonable to interpret the obvious relation of osteomalacia to undernutrition, poor hygiene, infections, and even to a disordered function of the endocrine glands which might interfere with the osseous metabolism.

Morbid Anatomy.—Typical osteomalactic bone is very soft, porous,

friable, and light as compared to normal bone. Characteristic irregular bending and fractures result. The bowing may be very angular with complete fractures when the process is confined to a portion only of the shaft. If the entire bone is involved the bowing may be broad and even. The outer surface of the bone is always quite uneven and the periosteum irregularly thickened, adherent, and injected. The cut surface presents almost no semblance of normal structure; it is yellow or reddish, and generally shows many areas of hemorrhage. The cortex is represented by a mere shell or may have entirely disappeared. Callus formation at the seat of the fractures is almost entirely lacking. Very little trabecular structure remains in the spongiosa; the marrow spaces are irregularly enlarged and filled with abnormal marrow. Small cysts are often seen. The epiphyseal cartilage is essentially unchanged and the joints are not involved, except as atrophy may ultimately take place.

Microscopically, the condition is most complex. It is evidently the result of a double process, *i. e.*, softening with absorption of old bone (halisteresis) and the formation of new uncalcified osteoid tissue.

The entire skeleton is sometimes involved, but the parts most commonly attacked are the pelvis, spine, thorax, and the long bones of the extremities. Under the weight of the body the sacrum is forced downward and at the same time the pelvis is compressed laterally, producing the so-called heart-shaped form. Similarly, as a result of softening in the vertebræ, the spine often becomes shortened and irregularly curved. Varying degrees of distortion of the thorax follow. Less marked but similar changes take place in the long bones of the extremities, more commonly in the femora and tibiæ. Any involvement of the skull is rare and if present no deformity follows.

Symptoms.—As the onset is insidious the disease is scarcely ever recognized until far advanced, in other words, until fractures and deformities appear. The most characteristic and constant subjective symptom is pain. It varies from a severe dull ache to an intense neuralgic type, and is usually located in the region of the affected bones. The pain is more intense at night and increased by movements or pressure over the bones. Tenderness to pressure over the bones is usually very acute. Muscle cramps and spasms with weakness sooner or later develop in the extremities, and are followed by atrophy. Fibrillary tremors, intensified reflexes, and disturbances of sensation may be present. When this disease is well developed the patient has a very peculiar shuffling, waddling gait. In the late stages of the disease locomotion is no longer possible and the patient becomes deformed into a helpless bedridden cripple. At this stage cachexia supervenes and the way is opened for many functional disturbances and complications. The course of osteomalacia may be very acute and cover a period of only a few months or extend over many years. Its duration in the puerperal form depends on the number of pregnancies. Remissions and even actual arrest of the disease have been reported.

The calcium content of the blood has been found to be increased. The amount of calcium and phosphates excreted in the urine is extremely variable and does not run parallel to the clinical course.

The bone abnormalities shown by *x*-ray are absolutely characteristic if the disease is well established. The outline of the bones is extremely faint and irregular with broad general curves or sharp angular deformities.

Transverse fractures of various types and degree are present, but with little or no callus formation. The cortex is of variable thickness, but for the most part thin, and the medullary cavity is dilated. The spongiosa appears very hazy and indistinct with evidence of general decalcification. Occasionally one or two small cysts are present.

Diagnosis.—The cardinal features of osteomalacia are unusually distinctive—its occurrence in young women particularly during pregnancy, the prominent and severe pain with tenderness over the bones, the peculiar deformities, and their characteristic distribution.

Osteitis fibrosa cystica may rarely resemble osteomalacia. This disease, however, begins almost exclusively during late childhood: the lesions are confined to the proximal ends of the long bones, much less of the skeleton is involved (often only a single bone), pain and tenderness are significant, and the changes in the bones are chiefly a fibrous metaplasia (general atrophy) combined with the formation of cysts. The *x*-ray findings are unlike those of osteomalacia.

Multiple myeloma contrasts with osteomalacia in that the ribs are the earliest and main focus of the disease. The blood and urine examinations afford important data. Pain and tenderness over the bones are common to both diseases, but otherwise the clinical pictures are quite unlike.

Rickets may be confused with osteomalacia in children, as in both diseases the most prominent features are softening and deformity of the long bones. In rickets, pain and tenderness are much less marked. The onset is in early childhood. The process is concerned primarily with osseous growth and the principal lesions are in the epiphyses. Finally the alterations in the skull, which are so characteristic of rickets, are lacking in osteomalacia. Roentgenographic studies are of great assistance in determining the nature of the bone lesions.

Senile osteoporosis, because of the frequent fractures, may suggest the senile form of osteomalacia; otherwise there is no resemblance between the two. The bones are hard and brittle in contrast to osteomalacia.

Treatment in the early stages of the disease is of the utmost importance since much more can be accomplished in the way of prophylaxis than cure. All that can be hoped for in any case is to arrest the progress of the disease.

The general hygiene of the patient is of the first importance. A full, nutritious diet, rich in calcium and phosphorus (milk, eggs, meat, fish, and vegetables), should be given. Very striking results following the use of animal fats (notably cod-liver oil) have been reported.

Pregnancy should be prohibited, and if necessary sterilization induced. Little can be said for the extravagant claims of drug therapy. One cubic centimeter of a 1 : 1000 solution of adrenalin injected subcutaneously every second day is strongly advocated by many, but its value is very doubtful. Phosphorus may be tried in combination with cod-liver oil (.05 .01 gm. to 100 c.c. cod-liver oil; 1 teaspoonful three to six times daily), or Pilulæ Phosphori, U. S. P. (1 pill daily).

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OSTEOPSATHYROSIS

(Osteogenesis Imperfecta, Fragilitas Ossium, Lobstein's Disease)

Definition.—Osteopsathyrosis is a rare congenital disease of the skeleton, the chief features of which are a generally deficient development of bone which leads to multiple spontaneous fractures of the long bones. Increased fragility of the bones, however, is associated with a great variety of diseases and should not be confused with this condition. A fetal, infantile, and adult form have been described.

Incidence.—Males and females are about equally affected. Familial predisposition is recognized, transmission usually taking place through the males, though in a few instances even through unaffected females.

Etiology.—The malady is clearly a nutritional disturbance which affects the skeleton during fetal life. No light has yet been thrown on the actual cause of the disease.

Morbid Anatomy.—The entire skeleton is delicate and fragile, but the bones most strikingly altered are the long bones of the extremities and the ribs. Normal growth in length probably takes place, but the diaphysis becomes greatly shortened in consequence of numerous fractures and angular bowing. In general, the bones are thin and delicate with the epiphyses not essentially altered. Bones with multiple fractures are very irregular in outline, with sharp angulations and a unique series of annular rings due to callus formation following fractures. So great is the fragility of the bones that fractures usually occur spontaneously or with only insignificant trauma. Both callus formation and healing are said to be normal. Flexibility of the bones is not increased. The head is of relatively normal size and shape, but the calcification in the calvarium is defective or in extreme cases entirely absent (calvaria membranacea).

The internal structure of the diaphyseal portion of the bones is greatly altered. The periosteum is very thin and shows no evidence of functional activity. The cortex is also thin and friable. Dilatation of the medullary canal and fibrous metaplasia of the marrow are present. The spongiosa may present few or no markings. The osseous tissue is poor in lime, but connective-tissue metaplasia does not seem to be a distinctive feature. In general, the process in the bones is a combination of high-grade atrophy and complete inertia of function.

Symptoms.—Constitutional symptoms are lacking. The chief features of the disease are the exquisite fragility of the bones and the deformities caused by the multiple fractures. The patient is usually a helpless cripple.

The *x*-ray demonstrates conditions which are particularly distinctive. The bones are of normal length except as they are affected by fractures, which, if numerous, produce marked deformities of an angular type. So faint is the shadow given by all the bones that they scarcely show any contrast with the adjacent soft parts. Variations in density often give a mottled aspect to the osseous tissue. Excessive callus formation is here and there present. The cortical layer of bone is thin, but variable in thickness and markedly deficient in lime. A dilated, irregular medullary cavity is present. The epiphyseal line is straight, and the cartilage thin

The results of metabolic studies have not been uniform, but indicate that there is no constant variation from the normal in the metabolism of nitrogen, calcium, magnesium, phosphorus, or potassium, although during

the active stage of the disease there is fairly definite evidence of a deficient calcium retention.

The vast majority of patients die *in utero* or shortly after birth. In the small percentage who survive through early infancy the frequent fractures lead to increasing deformity and resulting disability during the period of osseous growth. Fractures become less and less frequent as the individual approaches adult life, and are rare after the twenty-second year.

Diagnosis.—When the disease is typical its confusion with any other disease is hardly possible. Fractures do occur rarely in rickets and congenital syphilis, but in no other respects, either clinically or anatomically, do these conditions bear any semblance to osteopsathyrosis.

It has been suggested that there exists a possible relationship between this disease and achondroplasia, and the two diseases occasionally show a superficial resemblance. They are both congenital, but in achondroplasia the lesions in the bones result from a failure of enchondrial ossification, while in osteopsathyrosis they are due to the lack of normal function of the part of the periosteum and osteoblastic cells. The two are readily differentiated by the type of bony deformities and by the *x*-ray shadows.

Treatment.—A carefully regulated hygienic and dietetic regimen is always the first essential in treatment. Mechanical support is often serviceable as a precautionary measure to prevent fractures. Many *drugs* have been strongly recommended, among them arsenic, iron, calcium, and strontium, as well as thyroid, suprarenal, and pituitary preparations. A combination of phosphorus and cod-liver oil has been used extensively and has many enthusiastic advocates. Either phosphorus (0.01 gm.) or tribasic calcium phosphate (6 gm.) in cod-liver oil (60 c.c.) may be used. The daily amount recommended is 6 to 8 c.c. divided into 2 or 3 doses.

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ACHONDROPLASIA

(*Chondrodystrophia Fetalis*)

Definition.—Achondroplasia is a congenital disease of the bones which develop from cartilage and leads to a peculiar form of dwarfism. In consequence of this arrest in the development of the long bones of the extremities, patients with the disease have peculiarly distinctive characteristics, *i. e.*, normal trunk, disproportionately large head, "trident hands," and dwarfed and curved extremities.

Kaufmann describes three forms of achondroplasia: (1) *Chondrodystrophia hypoplastica* characterized by abortive cartilage growth; (2) *Chondrodystrophia malacia* (Chondromalacia fetalis) in which the predominating process is a softening of the epiphyseal cartilage; (3) *Chondrodystrophia hyperplastica* resulting from an overgrowth of the epiphyseal cartilage with resulting outward enlargement.

Incidence.—The disease is congenital and heredity plays a prominent rôle. Several achondroplastic dwarfs have been observed in one generation. Males are somewhat more common than females.

Etiology.—The inhibition of growth in the long bones is clearly the result of "an arrest or perversion of the normal processes of endochondrial

ossification." This dystrophy of the primoidal bone cartilage, according to Jansen, is caused by an abnormally small amnion, which, by reason of the increased hydrostatic pressure, leads to the arrest of growth of cartilage (dwarfism) and, by the infolding of the fetus, to the mechanical malformations (depression of root of the nose, changes in the diameters of the base of the skull, kyphos, etc.).

Morbid Anatomy.—The general deformities are unique. The fetus is a dwarf with an average length of 30 to 40 cm. as contrasted with the normal of 50 cm. The head is relatively large (brachycephalic type), the root of the nose is depressed giving the "pug nose" appearance, the lower jaw prominent (prognathus), the tongue thick and protruding, and the lips thickened. The circumference of the head often equals, or exceeds, the total length of the body. The trunk is well developed, but the extremities are short though usually well formed (micromelia). This results in the decentralization of the body, the central point being at the xyphoid instead of the symphysis pubes as normally. The hands are small and puggy. All of the fingers are tapering, of nearly equal length, and spread like the spokes of a wheel (*"main en trident"*). A striking peculiarity is the general thickening of the skin over the whole body and a folding especially over the joints.

Of the individual bones those usually affected, in order of their importance, are the femur, humerus, tibia, fibula, radius, ulna, pelvis, base of skull, bones of the hands and feet, vertebræ, and ribs. The long bones are massive in form and often slightly curved. An enormous hypertrophy of the epiphyses gives a mushroom appearance to the ends of the bones and frequently interferes with motion in the joints. The most characteristic lesion in the cartilage is a complete aplasia in the zone of ossification. In the diaphysis, endochrondal ossification is wanting while periosteal proliferation is active. The structure is grossly altered. Osteosclerosis and halasteresis are sometimes seen. Fractures may occur. Synostosis in the skull, pelvis, and other bones is common.

Symptoms.—The symptoms are largely objective, and have already been described. A vast majority of infants with this disease are still-born, death occurring from the seventh to ninth month of uterine life. The few who survive early infancy usually do not suffer any impairment of the general health and frequently live to old age. The fetal abnormalities of the skeleton are never altered. A peculiar feature of the disease is the abnormal development of the skeletal muscles which gives to the subject a strength much greater relatively than that of the normal individual. Mentally the subject is rarely subnormal. The sexual organs in both sexes show a normal or exaggerated growth. An increased sexual appetite is common and the achondroplastic women are said to be very prolific.

The *x*-ray findings are absolutely distinctive. The long bones are very short, massive, very dense, and with enormous increase in all the ridges for the attachment of muscles. A peculiarly characteristic deformity of the affected bones is the abrupt expansion of the epiphyseal end where the ossification is irregular and defective. Localized bowing, especially in the tibia and femur, is usual.

Diagnosis in typical cases is simple, as the unique features mentioned above sharply differentiate the disease from all other congenital affections of the skeleton.

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OXYCEPHALY

(Acrocephaly, Tower- or Steeple-head)

Definition.—Oxycephaly is an acquired disease characterized by a unique deformity of the head, high degree of exophthalmos, and more or less complete loss of vision. Fletcher gives a very complete description of this disease, of which he finds from 80 to 90 examples in the literature.

Incidence.—The disease is not congenital and in only a few instances is there any evidence of heredity. Males largely predominate among the subjects. There seems good reason to accept the opinion that the skull deformity results from premature synostosis of the coronal and sagittal sutures, but the cause of this early union is unknown. Fletcher suggests the possibility of a pituitary dystrophy.

Morbid Anatomy and Symptoms.—The general deformity of the head is striking. The forehead slopes gradually upward to a very pointed vertex on which the scalp is perched as though too small for the head. A flattening of the supra-orbital and temporal ridges, malar and supramaxillary regions is constant, while the cranial sutures show very early union. The paranasal sinuses are commonly rudimentary or absent. The orbits are greatly deformed and to a variable degree obliterated, while the sella turcica is enlarged. The hard palate is shorter and more arched than normal. Early caries of the teeth takes place. A considerable number of inconstant malformations of the ears, joints of the elbow and shoulder, fingers, and toes have been described. The brain shows evidence of compression.

The dusky, pale complexion, together with the characteristic mouth breathing, gives the patient a weird, vacant expression. Exophthalmos is practically constant, often amounting to actual dislocation, and since the lids cannot be closed, results in lacrimation and conjunctivitis. Nystagmus frequently occurs. Examination of the retina usually reveals a well-marked optic atrophy as well as tortuosity of the veins. Refractive errors are found. These ocular defects are progressive, and finally lead to a very marked impairment of vision or to complete blindness. The sense of smell may be lost, but the taste is rarely affected.

Headaches are the rule and may be of the most intense character. Vertigo is less prominent. Convulsions are described in a few cases in young children. The disease seems to have no effect on the duration of life.

Treatment.—Medicines are only useful for the relief of such symptoms as headaches. An operation for decompression is justified if severe symptoms of pressure develop.

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DISEASES OF THE NERVOUS SYSTEM

INTRODUCTION—METHODS OF EXAMINATION

It is impossible to understand nervous diseases without comprehension of general medicine and general pathology. The number of primary diseases of the nervous system is rather small, and degenerations due to defective hereditary endowment or vital lack are unpromising material for treatment. Infections such as the acute exanthemata, poliomyelitis, syphilis, or tuberculosis, however, may exert their most serious effect on the brain or spinal cord, and vascular degeneration is the cause of such simple and common brain lesions as apoplexy and cerebral thrombosis. Even central softening of the cord may be produced by sclerosis of spinal arteries if it be so severe as to impair nutrition of spinal nervous elements. The accurate appraisal of the powers of a failing heart muscle or the discovery of a starch indigestion may be the clue to the cause of senile epilepsy; and a high non-protein nitrogen content in the blood may throw light on obscure conditions such as recurring convulsions. The presence of hematoporphyrin in the urine may be evidence that an apparent "nervous breakdown" in an overworked middle-aged banker is really a chronic acetanilid poisoning from "Bromo-Seltzer" potation; and a high sugar content in the blood, although the urine is normal, may reveal the diabetic character of certain multiple neuritic and radicular pains which were previously unidentified and therefore irremediable. Neuritis of the brachial plexus is more often due to toxic absorption from a periapical dental abscess than to "exposure to cold." Absence of free hydrochloric acid in the gastric contents gives a lead to the correct therapy of pernicious anemia and combined system disease of the spinal cord in the fourth and fifth decade of life. The physician bent on correct neurological application must, therefore, like St. Peter on the roof top, call nothing common or unclean in his search for prime causes, and if he cannot culture the stool himself, must be aware of cultural possibilities and their significance. Just as a student must master a technic in order to diagnose a chest condition, must understand how to inspect, to percuss, to auscultate, and to weigh the positive and negative signs thus discerned, so he must know a simple method of approaching a neurological problem, an irreducible minimum of examination to be systematically pursued, which is based, as all examinations must be, on accurate anatomical and physiological knowledge.

It is not necessary to elaborate here the details of these fundamental sciences; but a plan of clinical approach may be outlined, with such application of our knowledge of structure and function as may be needed for illumination:

I. General impression. Attention. Memory. Emotional state. Delirium. Coma. Drowsiness.
II. Nervous system.
A. Organic:
1. Cranial nerves:
1—Sense of smell in each nostril: coffee; peppermint, etc.
2—Acuity; fields; fundi; scotomata.
3—4—6—Pupils: reaction; regularity of outline; ocular movements; diplopia; strabismus; nystagmus.
5—Motor-sensory, including cornea.
7—Muscles of expression; voluntary and emotional movements of face.
8—Cochlear: acuity; tinnitus. Vestibular; Bárány tests, etc.
9—10—11—12—Movements of tongue; palate; sternomastoids; trapezei; articulation.
Deglutition; gag reflex; tongue tremor.
Cords; laryngoscope.
2. Motor status:
(*a*) Head attitude; tremor, etc.
(*b*) Upper extremities: Power at each joint (grip with dynamometer). Tone; muscular nutrition. Adventitious movements. Tremor. Athetosis. Fibrillary twitching. Co-ordination, including deviation test. Speech; type of handedness.
(*c*) Trunk: Power of abdominal wall muscles.
Umbilical excursion.
(*d*) Lower extremities: as in upper extremities with addition of station and gait.
(*e*) Fits: Jacksonian or generalized.
3. Reflexes: Superficial; corneal, palatal, epigastric, abdominal, bulbocavernosus, plantar.
Deep: Jaw, wrist, elbow, knee, and ankle. Ankle and patellar clonus.
Organic: Micturition, retention, retention with overflow, incontinence. Periodic automatic incontinence. Defecation control. Priapism. Sexual potency. Urethral and anal sensations during sphincter relaxation
4. Sensory status: Subjective pain, direction of radiation, character, frequency.
Headache; tingling.
Sensibility to touch, pain, temperature, deep pressure pain, sense of position at joints. Vibration sense. Stereognosis. All abnormal areas to be charted pictorially.
5. Trophic functions: Skin, bullæ, herpes, bedsores, perforating ulcers. Glossy skin, erythema. Hydropathies.
B. Vegetative: Nervous system.
Cervical sympathetic; dilation of pupils to shade.
Ciliospinal reflex; proptosis; exophthalmos; enophthalmos; retraction of upper lid; pseudoptosis.
Flushing or sweating; angioneurosis. Raynaud's disease.
Erythromelalgia, transient edemata. Localized sweating.
III. Skeletal system. Abnormal projections and depressions.
Tenderness on percussion; immobility of spinal column.
IV. Gastro-intestinal system.
V. Respiratory system.
VI. Cardiovascular system with blood-pressure, etc. Temperature; pulse.
VII. Glandular system.
VIII. Laboratory data; blood and spinal fluid.
Summary.
Tentative diagnosis.

The general character of the complaint should first be determined so that the examiner may be oriented, to some degree, as to the nature of his problem; then a more careful history of the beginning and progress of the symptoms which led up to the final condition. This must be obtained as far as possible in chronological sequence, and should be as fully elaborated as the patient will permit. Some cross-examination is usually needed and lead-

ing questions may be delicately suggested; for example, transient attacks of diplopia, or of inadequacy of the bladder sphincter remote in point of time usually must be sought after, and similar direct questions often have to be made depending on how the trend of the history stimulates the diagnostic ideas of the examiner. The *position* of a lesion of the central nervous system is often determined by clinical examination which reveals precisely the nature and degree of the loss of physiological function, but its *nature* frequently can only be surmised by careful consideration of the manner in which such functions are interfered with. Four patients, for example, suffering respectively from luetic spinal thrombosis, extradural fibroma, Pott's disease (tuberculosis), and spinal fracture dislocation, all of which have involved to a severe degree the tenth dorsal segment of the cord, should have practically identical clinical manifestations and disabilities, spastic paraplegia (paralysis of both legs with increase in muscle-tone), complete sensory loss below the level of the affected spinal segment, and sphincter paralysis. These can be readily differentiated by the variations in historical detail. Complete paraplegia in the first instance would occur painlessly as an acute or subacute process, lasting but perhaps half an hour. In the second, probably one lower extremity would have symptoms, sensory and motor, for months before the other was involved, and even then complete paraplegia would probably take place slowly and be accompanied possibly by radicular pains confined to the skin area supplied by the tenth dorsal roots. In the third case, severe localized and shooting root pains would preface for a long time the rapid onset of signs of paraplegia. These pains are ameliorated by rest and increased by movement during the months in which the disease is confined to the bone and before the collection of inflammatory exudate so compresses the cord as to forbid transmission of impulses. The history of injury in the last instance would of course almost certainly reveal the cause of the paralysis.

After the previous personal and family history have been taken, the above scheme should be followed in the further conduct of the examination, but with discrimination, for one naturally does not examine visual acuity and the sense of smell before determining the picture in broader outline by appraising the proper functioning of the more important cranial nerves, and the motor, reflex, and sensory systems. It is usually wise to leave the examination of sensation to the last, because the condition of the other systems capable of more rapid investigation may indicate the probable character of the sensory derangement.

During the entire examination facts are gradually revealed which guide the physician toward this diagnosis or that. Consequently it is possible to stress some parts of the procedure more than others, to discover the futile lines of investigation, and to make the examination more forceful in other directions. Proper incidence in examination can only be learned by experience, and the student would do well at first to master the routine method already set forth.

The mental functions can be roughly judged by the taking of the history. The power of attention and concentration may be more precisely gauged by some such test as Bourdon's, in which the patient is asked to mark on a printed page a certain letter or letters. Should a suspicion arise of the patient's mental endowment, Ziehen's tests may be employed. Simple problems, such as explaining the difference between a river and a

lake, water and ice, an error and a falsehood, or further the Binet-Simon or Terman Scale may be employed, not slavishly, but with wisdom.

The first and second cranial nerves are really parts of the brain and not peripheral nerves, but it is convenient for clinical purposes to regard them as such. Visual acuity is tested roughly by asking the patient to count fingers with each eye separately. Accurate tests are made with Snellen's types. Changes in the size of the fields of vision can be determined roughly by seeing if the patient has as large a field of vision as that of the examiner; for accurate measurement a perimeter is necessary.

By *hemianopia* is meant blindness of half the visual field due to a lesion at the optic chiasma or behind it in one of the optic tracts. If the lesion be in front of the chiasma, *e. g.*, in the optic nerve itself, no hemianopia occurs because the decussation of the optic fibers has already taken place. Ipsolateral blindness results with optic atrophy expressed by an optic disk white as tissue paper when seen with the ophthalmoscope. Such lesions of the optic nerve may be due to a glioma of the nerve, or to pressure on the nerve by a subfrontal tumor or abscess, or by inflammatory exudate from sinusitis. Lesions of the chiasma itself are most often the result of tumor of the pituitary body, which by its position at the chiasma itself frequently gives rise to a bitemporal hemianopia and whitened papillæ.

Papillo-edema, choked disk, often improperly called optic neuritis, is the consequence of a rise of intracranial pressure, whereby cerebrospinal fluid is forced down the sheath space of the nerve and appears at the nerve head or papilla. This only indirectly affects the nerve and for a long time is compatible with perfect vision, but eventually the fluid becomes organized, the nerve-fibers are compressed, and secondary optic atrophy occurs. Primary optic atrophy may come from tabes or from poisoning with methyl alcohol. The constant use of the ophthalmoscope is essential in neurological medicine and almost essential in all branches of medicine. This instrument is more indispensable than a stethoscope.

Slight *irregularity in the shape of the pupils* always suggests that lues may have produced changes in the ciliary ganglion or in the ciliary nerves. Changes in the nuclei of the third nerve or in the ciliary ganglia may produce the classical *Argyll Robertson pupil*. This is ingravescent by the following stages:

1. A pupil contracting sluggishly to light and briskly on convergence.
2. One fixed to light and brisk on convergence.
3. One fixed to light and sluggish on convergence.
4. Fixed to light and fixed on convergence.

These phenomena are most often due to lues, but may be seen as a result of epidemic encephalitis, of acute alcoholism, or even of tumor, provided that the paths of the pupil reflexes be so slightly involved as to damage one set of fibers and not the other. The opposite of an Argyll Robertson pupil, *i. e.*, retention of the power of contraction to light and the loss of that on convergence is characteristic of diphtheritic nervous infection, but may also be occasionally due to periaqueductal lesions such as encephalitis.

The patient must be made to turn the eyes at different speeds in all directions, to reveal any strabismus, loss of ocular movement, nystagmus, or diplopia. Strabismus may depend on a long-standing refractive error, but if recently acquired is most probably due to paralysis of one of the ex-

trinsic ocular muscles and overaction of the unimpaired antagonist. For instance, a lesion of the third nerve may produce paralysis of the pupil, ptosis of the lid, and eversion of the eyeball from uncontrolled action of the unscathed external rectus muscle supplied by the intact sixth nerve. A slight paresis (weakness) of an ocular movement permits light to fall from a seen object on different parts of the two retinæ; this produces diplopia or double vision. The smaller the muscular error, the more distressing the diplopia seems to the patient, because with slight failure of parallelism in the eyeballs, the sensitive macular region of the retina, and the but slightly less sensitive perimacular region are in operation, so that the true image is very little more distinct than the false.

Loss of *conjugate movement* of the eyeballs may be discovered at this time due to some lesion of the quadrigeminal plate, such as a pineal tumor or encephalitis or even a midbrain luetic meningitis. This is occasionally seen also in myasthenia gravis. *Nystagmus* is an involuntary rhythmical ataxia or inco-ordination of the eyeballs, usually bilateral, and more often found on conjugate movement than when the eyeballs are stationary. In its true form it depends on a lesion of the cerebellum or its tracts in the pons, medulla, and midbrain. Lesions of these structures give rise to decomposition of rhythmic movements so that motor ataxia of the arms and legs results. This so-called intention tremor of the hands is a manifestation of pure cerebellar disease and is strictly analogous to the nystagmus of the eyeballs, caused by similar structural defects. Nystagmus may come from labyrinthine disease through the connections of the vestibular nerve with the cerebellar system by Deiter's nucleus, and it is occasionally present in somewhat different form in high myopes and albinos.

The fifth nerve has both a motor and sensory division; the former has its nucleus in the midbrain, the latter in the long descending nucleus in the medulla and first two segments of the cervical cord. On the course of the sensory division lies the Gasserian ganglion, below which passes the motor root. Total palsy of the sensory fifth destroys all superficial sensation on the same side of the face including the cornea, but excluding the skin over the jaw angle which is supplied by the great auricular nerve. The mucous membranes of the affected side are included in this anesthesia with the exception of the posterior third of the tongue, which receives its supply from the glossopharyngeal nerve. Taste is affected in that area of the tongue in which sensation is gone. The motor branch supplies the muscles of mastication, and when it is paralyzed the masseter and temporal muscles atrophy on the affected side, and the lower jaw when opened deviates to the side of the lesion by reason of the inaction of the ipsolateral external pterygoid muscle.

If the seventh nerve is affected in the pons there is usually also a lesion of the ipsolateral sixth nerve, due to the proximity of the sixth nucleus to the intrapontine seventh nerve. Paralysis of the nerve produces motor palsy of the same side of the face, and the forehead cannot be wrinkled, the eyelid properly closed, nor can the orbicular mouth muscles be used for laughing, whistling, or emotional expression. This paralysis renders eating and drinking arduous. Liquids are apt to be spilled owing to the difficulty in closing the lips. If the chorda tympani be involved, as when the lesion is in the Fallopian aqueduct, the sense of taste is affected in the anterior two-thirds of the same side of the tongue.

The eighth nerve consists of two sets of fibers having different functions; the cochlear branch from the organ of Corti, the nerve of hearing; and the vestibular branch from Scarpa's ganglion in the vestibular apparatus, the "nerve," as it were, by which movement and posture are appreciated. The cochlear function is examined by a ticking watch and by seeing if a vibrating tuning-fork is better heard by air or bone conduction. In deafness of middle-ear origin, the former is lost and the later retained. If the cochlear nerve be destroyed (so-called nerve deafness) both conductions are apt to be blocked.

Tests for the functional integrity of the vestibule consist in syringing the tympanum by hot and by cold water to see if nystagmus and vertigo be produced. Rapid rotation of the individual is also often valuable in this determination.

The functions of the remaining three cranial nerves are examined by making the patient protrude the tongue, and by looking carefully for such signs of muscular atrophy therein as tremor of fine "fibrillary" character, undue furrowing, especially unilateral, or deviation from the middle line of the teeth; by examining the movements of the palate on deep inspiration and phonation (the uvula in the presence of unilateral palatal palsy is lifted toward the sound side); by inspecting the vocal cords and determining if an abductor palsy be present due to involvement of the recurrent laryngeal nerve. The patient must be made to shrug his shoulders and rotate the head against resistance to discover a possible spinal accessory lesion giving rise to paralysis of the sternomastoid and upper third of the trapezius muscle.

The Motor System.—Inspection and palpation reveal loss of power in a muscle or group of muscles, and any changes in tone. The movements at each joint should be tested against resistance. The patient should extend the hands, abduct the arms, raise them above the head, grasp the observer's hands firmly, and show his power for pulling and pushing movements at the elbows. With the arms folded across the chest, he should try to rise from the bed; then all movements at the hip should be executed and appraised in power; likewise at the knee and ankle.

By palpation it is possible to estimate the nutrition of muscles; if it be diminished, the muscle is said to be atrophic; if increased, hypertrophic. Occasionally in certain muscular diseases (so-called myopathies) the apparent muscle-volume is increased while its power is greatly lessened (pseudohypertrophy).

The distribution of paralysis or paresis is determined by the site of the lesion. Thus, injury to one internal capsule produces hemiplegia or paralysis of the face, arm, or leg of the opposite side; injury to, say, the Pons, extensive enough to include both pyramidal tracts produces diplegia or double hemiplegia; a spinal cord injury is apt to cause paralysis of both legs or paraplegia, and, if it be in the cervical region, a tetraplegia, in which all four limbs are included.

The tone of muscles weakened by a lesion of the corticospinal motor tract (upper neuron palsy) is usually increased (spastic) and decreased (flaccid) when the lesion is in the motor system, between the anterior horn-cells and the motor end plate (lower neuron palsy). The characteristics of these two great types of paralysis may be further tabulated here:

Upper Neuron Palsy, Supranuclear Type.	*Lower Neuron Palsy, Nuclear and Infranuclear Type.*
"Movements" are paralyzed rather than single muscles or groups of muscles.	Single muscles or groups of muscles affected; if due to spinal lesion, in spinal segmental distribution.
Spasticity or increase of muscle tone.	Flaccidity or decrease of muscle tone.
No atrophy.	Atrophy the rule.
Reaction of muscles to electricity normal.	Electrical reactions those "of degeneration." No reaction to faradism, and an abnormally slow "vermiform" contraction to galvanism.
Deep reflexes increased. Arm-jerks, knee-, and ankle-jerks.	Deep reflexes decreased or lost
Plantar reflex of Babinski type; extension of great toe on stimulation of the sole of the foot.	Plantar reflex may be lost, but if present is of flexor type.

Tone and posture are influenced also by brain lesions not of the pyramidal or corticospinal system, but of the extrapyramidal or striatospinal system. This mechanism, phylogenetically older than the other dominating instrument, controls attitude, tonus, and automatic associated movements. The disease most characteristic of this lesion is paralysis agitans, in which attitude or posture of the body and limbs is altered; tonus is greatly increased so that the limbs when passively moved convey to the examiner a feeling of "cogwheel" rigidity; automatic associated movements (such as swinging the arms when walking) are decreased or lost, and tremor superadded by reason of interference with the rubrospinal tracts.

It has been stated above that the position of the lesion and the structures it affects determines the type of paralysis produced. Many combinations, of course, are possible, and while multiple lesions may occur in the brain and give rise to strange medleys of defective function, it is always wise for the beginner to determine shrewdly whether one lesion correctly placed could produce the existing condition. Thus, a hemorrhage in the crus cerebri produces paralysis of the contralateral face, arm, and leg, and almost certainly by its incidence on the third nerve, an ipsolateral ptosis of the eyelid, and defective movements of the pupil of that eye and of the superior, inferior, and internal rectus muscles. If the hemorrhage be large enough to implicate the red nucleus, the weakened arm and leg are ataxic and the seat of tremor. In similar fashion, a unilateral pontine lesion may produce contralateral hemiplegia and ipsolateral palsy of the fifth, sixth, seventh, and eighth nerves. Bulbar lesions naturally interfere with the functions of the cranial nerves therein, so that there is trouble in swallowing, in articulating, or in phonation.

A lesion, for example, of the seventh cervical segment of the cord produces spinal level signs of lower motor neuron type, with interference with the functions of the seventh segment, *e. g.*, paralysis of the intrinsic hand muscles with retention of movements at the shoulder (supplied through the fifth and sixth segments) and pyramidal tract paralysis (upper motor neuron type) below the lesion level; that is to say, spastic paraplegia with sensory paralysis below the distribution of the seventh segment, diminished arm-jerks, and increased deep reflexes in the legs. Sphincter paralysis also occurs.

A middorsal lesion gives rise to spastic paraplegia also; the arms are not implicated, but owing to the long innervation of the rectal abdominal muscles from the dorsal cord, the upper recti remain intact while the lower

are paralyzed. The attachment of the umbilicus to the sheath of the rectus muscle determines then in this situation that on attempts to contract the recti muscles (as in rising from the recumbent position) the umbilicus will not remain stationary as it does normally, but will be pulled upward 1 or 2 inches by the unantagonized superior recti muscles.

A lesion of the cauda equina produces a picture determined by the functions of the nerve roots contained in the lowest part of the spinal dura mater sheath. The motor loss is of lower neuron type, characterized by atrophy of the affected muscle group with electrical reaction of degeneration and loss of the deep reflexes subserved by the roots affected. If the sacral roots be involved there is usually sphincter paralysis and, in any case, if posterior spinal roots be included in the damaged area there are characteristic shooting "root" pains. Such loss of sensation as may be present is found in the skin areas sensorily served by the affected roots.

The paralysis consequent to inflammation or injury of any nerve or plexus of nerves is, of course, of lower neuron type, and is confined to the muscles supplied by the affected nerves.

Multiple neuritis due to some general constitutional intoxication (alcohol, lead, diphtheritic toxin, diabetes, lack of vitamins (beriberi) is a symmetrical disease which produces dropped hands and dropped feet, and is due to the especial incidence of the poison on the extensors of the fingers and hands and the anterior tibial and peroneal muscle groups. The palsy is flaccid and atrophic with loss of reflexes, and is usually associated with pain in the affected muscles and loss of sensation, following "a glove and stocking" distribution due to the failure of function in the terminal twigs of the mixed peripheral nerves.

During the examination of the motor system myopathies must be looked for. These are primary muscular diseases which occur in predisposed stocks. The cause is unknown; the peculiar distribution of the muscular weaknesses, the absence of changes in reflexes (other than from mechanical reasons due to extreme muscle atrophy), and of sensory changes combined with the presence of pseudohypertrophy in certain muscles, especially those of the calves and infraspinati due to the fatty changes in the degenerating muscle, usually give the clue to correct diagnosis.

Ataxia or inco-ordination of the arms is sought for by asking the patient to bring his finger-tips together with the arms extended before him, to touch his nose or his ear with each index-finger, and to follow with his hands the movements made by the observer's finger. The first two tests are carried out with the eyes open and shut. Ataxia of gait is tested by asking the patient to walk along a straight line, and to stand still with the feet together and the eyes shut. This is known as Romberg's test. Ataxia may depend on loss of sensation from the affected limb, especially on loss of the sense of position, such as occurs typically in disease of the posterior columns like tabes dorsalis. The patient is able to guide the limb by the eyes, but in the dark, or if the eyes be shut, he "loses" the limb, does not know exactly its position, and brings it, smoothly enough, to the wrong place. This form of ataxia thus arises from a purely sensory defect whereby inadequate information is received.

The other great class of ataxias is entirely motor in origin, and is due to a defect in the cerebellum or its tracts. The function, roughly speaking, of this organ is to compose, to make smooth, cortical impulses. When this

function has been impaired, the movement of the limb is broken up into its component parts and becomes jerky. The patient is always aware of the position of the limb in space, but he lacks the controlling mechanism to bring it smoothly and with properly graduated forces to its objective. This failure to synchronize muscular action is known as asynergia, and results not only in the jerky movements described, but in dysmetria, which consists in overshooting the objective because of failure to control nicely the strength required for the task. Dysmetria may occur, though with a different aspect, in ataxia of sensory origin. In this the spatial relationship between the limb and the objective is poorly estimated and the wrong movement is well performed.

The gait of a "sensory" ataxic is stamping in character. The tabetic is constantly in the position of a normal person who on going up a flight of stairs in the dark thinks there are eight steps when there are but seven. He miscalculates the distance between his foot and the ground in a way the tabetic does all the time. A cerebellar gait is more reeling or "drunken." If only one cerebellar lobe be affected the ataxia is on the same side as the lesion, and the patient tends to fall to that side. This ipsolaterality of cerebellar ataxia depends on the fact that each cerebellar lobe "controls" impulses coming from the opposite cerebrum, which in turn sends impulses to the opposite side of the body through the decussation of the pyramids.

Under the heading "involuntary movements" are classified chorea, the jerky non-proposive character of which has a definite cerebellar quality; athetosis, slow vermiform movements which occur in a hemiplegic limb in the producing lesion of which a thalamic component has occurred; fibrillary twitching, fine rippling movements of parts of the muscular bellies which occur typically in amyotrophic lateral sclerosis, but which are indicative of all acute degeneration and impending or progressive muscle atrophy; myoclonus, in which an entire muscle or muscle group is twitched, often rhythmically and violently seen in both acute and chronic epidemic encephalitis, as a release phenomenon from the basal ganglia of the same general pathological pattern as athetosis; and tremors, fine, such as are seen in exophthalmic goiter, or coarse, from lesions of the tegmentum of the pons or crus with changes in the rubrospinal tracts.

The **reflexes** are divided into the superficial, the deep, and the organic types. In the first group the corneal has already been considered. The pharyngeal and palatal reflex consist of contraction of the pharynx and elevation of the palate when either is touched, and depend for their production on integrity of the glossopharyngeal nerve and the bulb. They may be entirely absent in hysteria and in the absence of organic disease.

The abdominal reflexes are obtained by stroking with some hard instrument (a pencil or key) parallel with the ribs, and also with the inguinal folds. Their spinal level runs from the eighth to the twelfth dorsal segments. They are very rarely absent in healthy young or middle-aged persons whose abdominal walls are not obese. If bilaterally absent in young persons, a suspicion of early multiple sclerosis may be entertained. In cerebral hemiplegia the abdominal wall (transversalis, rectus abdominis, and internal oblique muscle) usually does not contract on stimulation on the paralyzed side; and reduction of the force of this reflex on one side is often early intimation of a slight or ingravescent lesion of the motor tract supplying that side.

The cremasteric reflex, elevation of the testicle on stroking the inner side of the thigh, is less dependable than the abdominal reflex. It may be retained in the presence of a complete hemiplegia, but is more probably reduced or lost. Its segmental level is the first and second lumbar.

The most important superficial reflex is the plantar. To evoke this the blunt instrument is stroked with some force along the outer side of the sole from behind forward. Normally this is followed by a flexor movement of the great toe and a contraction of the tensor fasciæ femoris. Care must be taken not to overstimulate, as this produces a defensive withdrawal and dorsiflexion of the foot. If the motor tract or the leg center in the cortex be injured, this normal flexor type of plantar reflex is replaced by a slow extensor movement of the great toe, a "fanning" spread of the other toes, and a contraction of the hamstring muscles. This extensor reflex is the so-called Babinski sign. It is always pathological, being a more primitive type of spinal reflex than the flexor response and is normally controlled by the cortex. It is physiologically present in infants unable to walk. It may occur for a few minutes to an hour after an epileptic convulsion sufficiently severe temporarily to exhaust the cortex.

The bulbocavernosum reflex is elicited by placing the finger on the urethra behind the scrotum and at the same time stimulating by pin prick the glans; normally the urethra is felt to contract sharply. This phenomenon is lost early in tabes dorsalis, and is abolished by any lesion of the caudal roots of the third and fourth sacral segments.

The Deep Reflexes.—The biceps, triceps, and supinator jerks depend on the integrity of the reflex arc through the fifth cervical to the first dorsal segment. They are obtained by tapping the biceps tendon, the styloid process of the radius, and the triceps tendon.

The knee- and ankle-jerks, obtained by tapping the patellar and achilles tendons when the supporting muscles are entirely relaxed, have segmental levels of third and fourth lumbar and first and second sacral respectively. If feeble they can be increased by making the patient lock his hands together and pull one against the other. They are abolished by any break in the arc; by multiple neuritis where the break occurs low down in the peripheral nerves; by tabes dorsalis, Friedreich's ataxia, or subacute combined sclerosis of the cord, the lesion here being in the posterior roots or columns of the cord; by disease of the motor anterior horn-cells of the cord, as in acute poliomyelitis and amyotrophic lateral sclerosis; or occasionally by cavity formation in the cord (syringomyelia). As has been said myopathies may abolish the reflex by destroying the muscular mechanism needed for their production. These reflexes are exaggerated in the presence of pyramidal tract disease, in which case the normal cortical control of the cord is withdrawn so that the cord is allowed independent action.

Increased deep reflexes, unless unilateral, are not as valuable a sign of organic disease as is their loss. When these reflexes are increased one must look for ankle clonus, a rhythmical contraction of the soleus muscle obtained by continued passive stretching of the achilles tendon. The organic motor reflexes depend on the vegetative nervous system and cause contraction for the most part of non-striated involuntary muscles. The most important are the ciliospinal, whereby the pupil dilates on scratching the skin of the neck; and the oculocardiac, whereby the heart is slowed some

ten beats a minute by compression of the eyeballs in their sockets. This is especially marked in vagotonic persons and may be abolished in tabes.

The reflex centers of the vesical, rectal, uterine, and genital automatic actions are in the lumbar and sacral segments of the cord, and also in the hypogastric and hemorrhoidal plexuses of the vegetative nervous system. Periodic reflex bladder incontinence is normal in infancy; after total transverse spinal cord lesion there is an initial period of urinary retention followed in a week or two by overflow dribbling, and a week or two later by the establishment of a reflex automatic bladder action, whereby the bladder content is discharged periodically by the production of a primitive mass reflex in response to stimulation of the sole or the inner side of the thigh.

Sensation.—It would be well here to recollect in outline the paths in the central nervous system of the various forms of sensation. These pass upward from the periphery to the posterior roots of the cord; thence they pass into the cord and are distributed as follows: The fibers bringing sensation from the muscles and joints, together with a few of those for touch, pass upward uncrossed in posterior columns to the gracile and cuneate nuclei on the same side of the medulla as they entered the cord. Thence they continue upward and cross the middle line in the internal arcuate fibers forming the sensory decussation of the fillet. The fibers continue through the crus cerebri to the optic thalamus, where redistribution again takes place, some ending in the thalamus, others continuing to the rolandic area of the cortex.

The remainder of the tactile fibers and those conveying temperature and superficial pain sensations entering by the posterior root cross the spinal cord almost immediately and go up the opposite side of the cord from which they entered in the spinothalamic tract of the lateral column. When they reach the thalamus the same redistribution takes place, as has been mentioned. Some impulses pass on to the discriminating centers of the postrolandic and supramarginal gyri; others end in the nuclei of the thalamus, which in this manner is a terminus for various types of undiscriminating sensation of an emotional character (pleasure, pain, and some visceral sensations).

To recapitulate, the sensations of deep pressure pain (such as that produced by squeezing the calf muscles), of vibration (ability to appreciate the vibration of a tuning-fork placed on bone), of sense of position of joints (whether they be flexed or extended), and some touch sensations, ascend the same side of the cord as they enter on, to relay stations in the posterior column nuclei in the medulla. From there they cross to the opposite side in the fillet to the optic thalamus, and either end or are relayed to the sensory cortex.

Sensations of temperature (distinguishing between hot and cold), of superficial pain (pin prick), and the majority of superficial touch sensations enter the cord as do the others, by the posterior roots, cross the cord immediately, and ascend to the thalamus in the lateral ground bundle or lateral column, where they are dealt with as already described.

These sensations do not reach the cortex as pain, temperature, touch, etc.; at this highest level judgment and selection of sensation occurs, whereby spatial relations and differentiation of objects (stereognosis) and discrimination of intensity takes place.

It is well here to set down, if only as a method of remembering the

functional anatomy of the cord, the symptom-complex known as Brown-Séquard's paralysis produced by a lesion destroying one lateral half of the cord. On the side of the lesion, from section of the descending pyramidal tract, there will be upper motor neuron paralysis of the leg with increased deep reflexes and an extensor type of plantar reflex. From section of the posterior columns and interruption of the uncrossed fibers from the posterior roots below the lesion, there results, on the side of the lesion, loss of sense of position of the limb, loss of vibration sense, and loss of

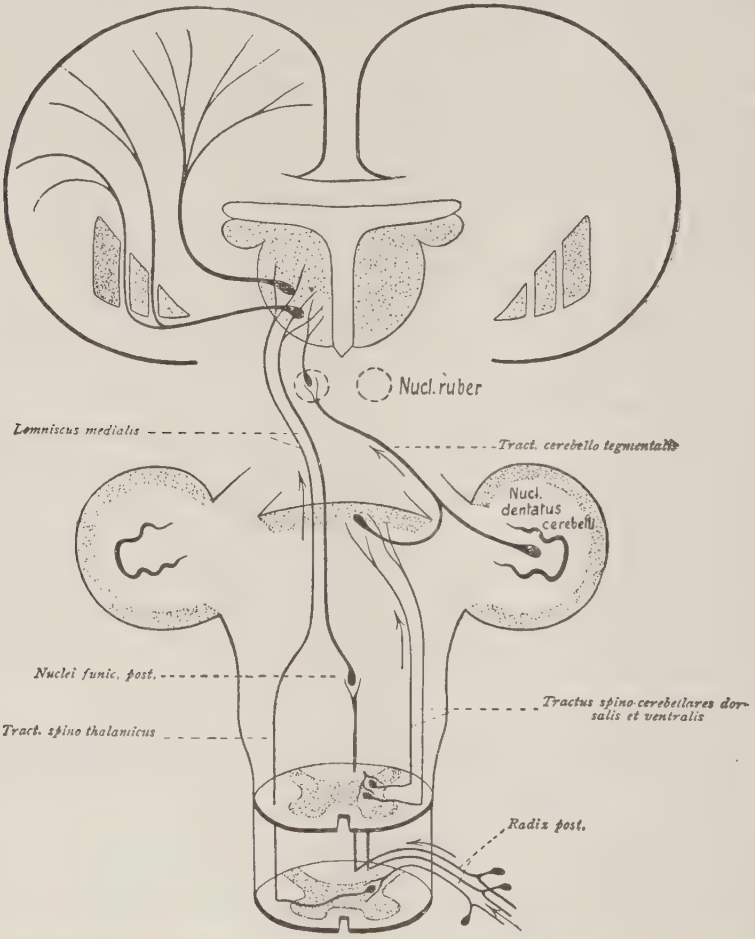

Fig. 25.—Chief sensory pathways ascending from the spinal cord. (Villiger's Anatomy of the Nervous System.)

deep pressure pain sensations. At the level of the lesion there is an ipsilateral zone of loss to touch, temperature, and superficial pain, due to interruption of the local fibers of the posterior roots.

On the body opposite to and below the lesion there is loss of sensation for temperature and superficial pain and some depression of touch appreciation, due to the cutting of the spinally crossed fibers for these functions coming from the opposite side of the cord. There will be no motor paralysis on this side.

The beginner would do well to avoid complicated instruments for sensory examination; a pin, a wisp of cotton, a tuning-fork, and two test-tubes of hot and cold water, added to intelligence and patience, is adequate equipment. Knowledge of the types of sensory loss may be added to this armament; the skin areas served by the plexuses and the peripheral nerves, the spinal root areas, and familiarity with the phenomenon of dissociated sensation, which has just been described as occurring in Brown-

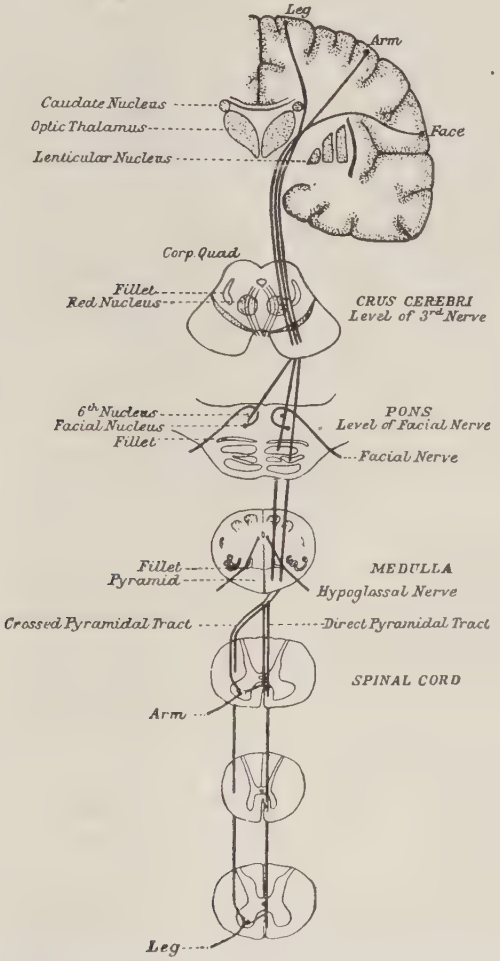

Fig. 26.—Diagram of the pyramidal tract. (The chief motor pathway of the nervous system.) (Purves-Stewart's Diagnosis of Nervous Diseases.)

Séquard palsy, and is also seen in syringomyelia (central lesion of the cord, involving pain and temperature fibers at the point of their spinal decussation, but sparing the other sensory fibers less centrally placed).

The examination of the trophic functions or, as they are still called, the trophoneuroses, is best understood from the chapter on those conditions. The same is true of the examination of the cerebrospinal fluid, of aphasia,

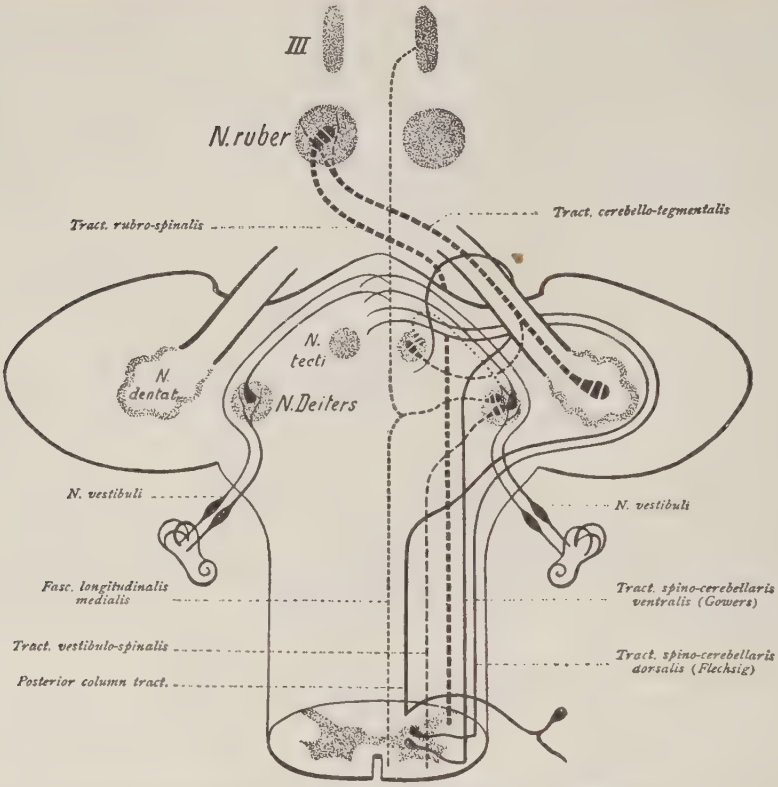

Fig. 27.—Important pathways to and from the cerebellum. (Villiger's Anatomy of the Nervous System.)

and convulsions. The vegetative nervous system is dealt with, as far as our clinical knowledge of its functions is concerned, in the section on endocrinological conditions.

FOSTER KENNEDY.

THE DIAGNOSTIC SIGNIFICANCE OF THE CEREBROSPINAL FLUID

History.—The study of the cerebrospinal fluid, which now embraces physical, histological, chemical, bacteriological, biological, and immunological methods, had its beginnings only thirty-five years ago, when Quincke demonstrated his method of lumbar puncture. This has remained practically unaltered to the present time. The first punctures were performed for therapeutic purposes, to reduce pressure in hydrocephalus and tubercular meningitis. Soon afterward fluid was also withdrawn in acute meningitis.

Following close on the diagnostic and therapeutic application of lumbar puncture in meningitis, the procedure was employed on patients with

syphilis of the nervous system so that the fluid might be examined. But in the first decade of this century the only criteria of value were the cell count, differential cell picture, and globulin reaction. In this pioneer work the French workers, Ravaut, Sicard, and others, led the way. In 1912 Mestrezat published his epoch-making book which emphasized the chemical aspect and laid the foundation for much subsequent work. At this time the Wassermann reaction took its place with chemistry, cytology, and bacteriology, and the diagnosis of neurosyphilis became clarified by the demonstration of the "four reactions of Nonne," namely, a lymphocytosis, an increase in the globulin content, and a positive Wassermann reaction in the blood and in the spinal fluid.

Colloidal chemistry entered the field in 1913 with the publication of Lange's gold chlorid test. The gold-sol test attracted immediate attention, and, as it now seems, assumed unwarranted importance; it certainly led to neglect of the previously known fundamental tests.

Little attention had been paid to pressure, although Quincke in his original work used a manometer. Since Queckenstedt's article on hydrodynamic tests appeared in 1916, however, pressure studies at the bedside have been added to the tests carried out in the laboratory.

Recently attention has been called to "fractional" examinations of the spinal fluid, that is, examination of the first and last portions of fluid obtained on lumbar puncture, to obtain evidence of the locus of pathology. The value of this method has, however, been promptly lost, because there are more striking differences in fluid at different loci of the ventriculosubarachnoid spaces which can be demonstrated by cisternal and ventricular punctures.

The present advance in our knowledge of the cerebrospinal fluid as indication of disease appears to be largely in the field of chemistry, with close correlation of blood and fluid by means of recently devised microchemical tests. Application of these tests to the fluid obtained from different points and synchronously with the blood, bids fair to reveal fundamental physiology of the nervous system, in both health and disease.

Anatomy and Physiology.—The cerebrospinal fluid is found in the ventricles of the brain, the subarachnoid spaces of the brain and spinal cord, and, according to some observers, in the perivascular spaces. The normal amount is approximately 150 c.c.; under abnormal physiological and pathological states this amount may be very considerably increased. While the whole fluid system is intercommunicable, the fact that the composition of the ventricular fluid differs considerably from that of the subarachnoid space is evidence that admixture is not prompt or complete.

According to Weed, there appears to be a dual source of the fluid, although whether it is a secretion, a filtrate, or a dialysate is not certain. Most of the fluid appears to come from the choroid plexus of the lateral ventricles, whence it passes through the third ventricle and aqueduct of Sylvius into the fourth ventricle, and then by way of the foramina of Magendie and Luschka into the cisterna magna to mix with a smaller amount of fluid, which seeps into the cerebral subarachnoid space by way of the perivascular spaces. The exact point of origin of this latter fluid is in doubt. From the cisterna magna, which Dandy describes as the "distributing center," the cerebrospinal fluid passes forward along the base of the brain and upward over the convexities, where it is absorbed into the venous sinuses by means

of the arachnoid villi. There is also a downward course into the spinal subarachnoid space, whence it is in part absorbed by the arachnoid projections which cover the spinal nerves.

Movement of the fluid must not be thought of as a stream or a flow, but as admixture and diffusion, affected by variations of pressure caused by pulse, respiration, etc. Normally slow movements of fluid from one locus to another may be rendered quite rapid under artificial conditions of pressure and drainage, although they are always more rapid when in the direction of the normal trend.

Only one function of the cerebrospinal fluid is known, the mechanical protection of the brain and spinal cord. That it also serves metabolic functions is likely, but what these are and how they are performed is not known.

Loci at Which the Cerebrospinal Fluid May Be Obtained.—Long before fluid was obtained by design, occasional opportunities were offered for its examination in cases of rhinorrhea following fracture of the cribriform plate. This accident is rare and examination of the fluid of little value except as it indicates the large potential output (approximately 1 liter a day). Since 1891 fluid has been obtained for diagnosis primarily by lumbar puncture. The needle enters the caudal end of the subarachnoid space below the conus, which lies opposite the first lumbar vertebra: in this space, occupied only by the roots of the cauda equina, nerves cannot be injured, for it is impossible to prick a nerve floating in fluid. There are five interspaces at which lumbar puncture may safely be made, the most convenient of which may be used in any given case. Two other loci at which cerebrospinal fluid can be obtained should be used only in certain emergencies, such as blocking of the spinal subarachnoid spaces during meningitis. These are the *cisterna magna* and the *lateral ventricles*, and they may be readily and safely punctured by operators with sufficient training.

Tests.—Among the many tests which have been recommended in studying the cerebrospinal fluid a few stand out as of proved value. With 10 c.c. of fluid, or even less, all of the most important may be performed, and fortunately several of the most significant can be carried out literally at the bedside. A number of special examinations are also of value in certain investigations, but it is the writer's opinion that the results of the following group of tests, when carefully analyzed and correlated with the clinical findings, give reliable and valuable information.

Physical Characteristics.—The fluid which is normally crystal-clear may be turbid from bacteria or cells, or actually purulent. The formation of a clot on standing indicates that fibrin is present and is always pathological. Purulent fluid may be yellow, green, white, or muddy, according to the bacteria present. A clear yellow coloration is produced by pigment from the blood, and may indicate antecedent hemorrhage or venous stasis characteristically due to compression of the spinal cord. Whether disease or technic is responsible for blood-tinged or bloody fluid must be at once determined. (See below.)

Pressure and Dynamic Studies.—Normal pressure, with the patient in the lateral position and completely relaxed, is usually between 100 and 200 mm. in the aqueous manometer. For clinical purposes this may be measured with sufficient accuracy by allowing the fluid to run into a glass tube with a 2 mm. bore. A pressure above 250 mm. is suspiciously high,

and above 300 mm. almost always denotes increased intracranial pressure. Low pressures have no certain significance. The manometer demonstrates pulse oscillations and respiratory excursions, the former usually 1 to 2 mm., the latter 4 to 6 mm. in extent.

With the manometer in place and oscillations visible, an assistant presses gently on each side of the larynx until the carotid pulse is palpable. By this maneuver, which compresses the jugular veins, venous stasis is immediately produced in the cranium; this results in increased intracranial pressure which, under normal conditions, is transmitted promptly throughout the cerebrospinal fluid and is registered by a marked and prompt rise in the lumbar manometer. This test is useful in the diagnosis of a number of conditions leading to spinal subarachnoid block, tumors of the cerebellar fossa, and lateral sinus thrombosis.

Cytology.—One of the earliest tests employed and still one of the most important examinations is that of the cell content of the fluid. Normally no cells are present, or only a rare arachnoid cell. Some observers maintain that as many as 10 lymphocytes per cubic centimeter of fluid is normal, but the writer thinks that the presence of 10 lymphocytes, or even 5, is pathological and requires explanation.

A count of more than 10 lymphocytes is almost universally admitted to be pathological, and to be evidence of an inflammatory process somewhere within the cerebral or spinal subarachnoid spaces. A certain value is attributable to high and low counts, as will appear in later sections. The count should be carefully obtained from well-mixed freshly drawn fluid in the regular blood-counting chamber under the high-power objective. This permits identification of the cells.

Differential counting of cells is simple in acute exudative fluids by means of ordinary stained films, but in fluids containing few cells it is difficult, because the cells are readily lost in the process of making the film, and often stain poorly on account of distortion due to prolonged immersion in the fluid. At least three types of cells should, however, be recognized, even in the counting chamber—the lymphocyte, the polymorphonuclear leukocyte, and the large arachnoid mononuclear cell. With special care plasma cells and eosinophils may be identified, and tumor cells have occasionally been reported present. The significance of cell types, as well as of cell numbers, is obviously great.

Chemistry.—*Protein determination* in the cerebrospinal fluid is of fundamental importance. Normally very slight (20 to 40 mgm. per 100 c.c.), the protein content may increase pathologically (up to 4 gm. per 100 c.c.) until it approaches that of blood-serum. This must be looked upon as a non-specific reaction of exudative or transudative origin. Rough examination with the naked eye is of value when once the examiner has learned the normal turbidity. The nitric acid, trichloracetic acid, and other tests demonstrate the presence of coagulated protein, but perhaps the most simple of all is the mixture of 3 parts of 95 per cent. alcohol with 1 part of spinal fluid. This normally produces a faint protein flocculation easily recognizable from the precipitation of pathological amounts. So great is the importance of even a slight protein increase that a quantitative estimation is desirable; for this purpose the sulphosalicylic acid method of Denis is recommended.

Unquestionably, quantitative *estimation of the globulin and albumin*

contents separately will be of value when reliable microchemical tests have been perfected. At the present time the globulin ring test of Ross-Jones (saturated solution of ammonium sulphate underlying an equal amount of spinal fluid) gives a rough index of the amount of globulin present. Normally no cloud is seen at the junction of fluid and reagent, but in neurosyphilis in particular a well-defined cloud indicates a marked globulin increase, even when the total protein content (*i. e.*, albumins and globulins) shows no great increase by the sulphosalicylic acid method.

Sugar.—Normally the lumbar fluid contains about .05 per cent. sugar. It is now well determined that a diminution or even a loss of sugar occurs regularly in acute meningitis and tubercular meningitis. An increase in the sugar content appears to be characteristic of at least one disease, epidemic encephalitis. Quantitative tests for sugar when these diseases must be considered in diagnosis are therefore necessary. A rough, macroscopical method is here of little value, although failure of Benedict's solution to reduce with 3 drops of fluid suggests a diminution in the sugar content.

Chlorids.—The chlorid content seems to be regularly low in acute and subacute meningitis.

Non-protein Nitrogen, Urea, Uric Acid, and Creatinin.—Tests for non-protein nitrogen, urea, uric acid, and creatinin are occasionally made, for example, in uremia, but are not recommended as of routine value.

Colloidal Tests.—Three colloidal tests have been widely recommended: the original test of Lange using *gold chlorid;* the *gum mastic test* of Emanuel; and the more recent *benzoin test* of Guillain.

The mechanism of precipitation by these tests is not understood, but certain changes occur with different dilutions of spinal fluid which are more or less characteristic of a number of diseases. The earlier workers unquestionably assigned to these tests, particularly the gold-sol test, altogether too much value. One type of curve in the gold-sol test has, however, retained its importance, namely, the misnamed "paretic curve." This type of reaction, represented by discoloration of the gold chlorid reagent by the stronger dilutions of spinal fluid, and by complete precipitation of the benzoin and mastic test reagents, is certainly characteristic of paresis, although it is not pathognomonic. Like others, the colloidal tests have a distinct place in the complete analysis of the spinal fluid. Alone they are of little value.

Biological Test.—The Wassermann test.

Bacteriological Tests.—As in the study of other fluids and exudates, by means of films and cultures. Guinea-pig inoculations for tuberculosis, rabbit inoculations for treponema pallidum, and monkey inoculations for poliomyelitis, must be considered as exceptional or research procedures, and not applicable to routine examination of the fluid.

Summary.—When diagnosis is doubtful and the spinal fluid is to be examined, the routine procedure should be to perform lumbar puncture with the patient in a lateral horizontal position; take the initial pressure reading with an aqueous manometer; observe the increase of pressure during compression of the jugular veins, and the rapidity and degree of fall after release of the jugular veins; and to observe the pressure after withdrawal of 10 c.c. of spinal fluid so that the difference between the initial and final readings may give some indication of the total quantity of fluid in the cerebrospinal spaces. In the laboratory the cell count and differential cell count should be determined, the protein content ascertained by the

quantitative method if possible; the globulin ring, colloidal (preferably gold-sol or benzoin), and Wassermann tests made; and the sugar content determined quantitatively if the fluid has not stood too long. Bacteriological studies are desirable if there is turbidity or if meningeal infection is strongly suspected.

Clinical Application of Tests.—Let us now consider the diseases and pathological conditions which evoke positive changes in the spinal fluid. Because of striking similarity in fluid pathology these may most easily be compared in groups, irrespective of their etiology. This method also emphasizes any contrasts within a given group.

1. The Acute Meningitides.—By the time that *acute meningitis* is suspected clinically, the spinal fluid has usually undergone characteristic changes, *i. e.*, increase in pressure, increase in the number of cells (polymorphonuclear leukocytes predominating), increase in the protein content, and invasion by the infecting organism demonstrable both on film and culture. The fluid, at first merely cloudy, rapidly becomes more turbid and purulent, contains increasing numbers of organisms and cells and an increasing quantity of protein and fibrin either preformed or forming in the test-tube. Sugar estimation is of great significance in all forms of acute meningitis. The content is reduced early and rapidly falls to zero, a condition unknown in other diseases. It should be emphasized that this test must be performed immediately after aspiration of the fluid because the sugar disappears *in vitro*.

While the infecting organism is usually found with ease, particularly the pneumococcus and streptococcus, the meningococcus frequently cannot be recovered in the early stages of the disease even in the centrifugalized sediment. In such cases a number of procedures are recommended: the spinal canal may be drained to permit recovery of the organism in the last portion of fluid; the neck may be rotated to loosen the exudate which tends to accumulate about the foramen magnum; puncture of the cisterna magna may be employed; and finally puncture of a lateral ventricle. All of these methods have been employed successfully for recovering the organism and for administering serum.

In acute meningitis which has entered into a subacute stage there is a tendency for mucofibrinous masses to accumulate in different loci of the spinal and cerebral subarachnoid spaces, especially in the lumbar sac and in the upper cervical canal. Under such conditions the fluid is thick, purulent, and scanty. The organisms may be numerous or be destroyed. In such cases puncture must be made at another locus.

Numerous organisms attack the meninges, but by far the most common are the streptococcus, pneumococcus, and meningococcus. In epidemics the latter assumes first place in frequency. Other bacteria less frequently recovered are *Staphylococcus aureus* and *albus*, *Bacillus pyocyaneus*, *B. influenzæ*, *B. typhosus*, *B. coli*, and *Micrococcus catarrhalis*. As a rule, the meningitis caused by these less frequent organisms is of a less severe type, but variations in the virulence of different strains make such a statement of only general significance.

Under certain conditions *aseptic meningitis* develops. The condition of the fluid is similar to that of acute bacterial meningitis, except for the absence of infecting organisms and the normal sugar content. Aseptic meningitis develops in certain fevers, such as pneumonia, and is thought

to result from the action of a toxin which passes into the cerebrospinal spaces. It occurs regularly after injection of foreign substances into the subarachnoid space and is, therefore, a sequela of intraspinal injection of serum. Lipiodol, recently introduced for radiographic localization of tumors of the spinal cord, causes a well-marked transitory aseptic meningitis with symptoms of meningeal irritation. Even salt solutions, not properly balanced, cause a reaction which may be classified as aseptic meningitis.

2. Tuberculous Meningitis, Acute Poliomyelitis, Epidemic Encephalitis, Brain Abscess.—In tuberculous meningitis, acute poliomyelitis, epidemic encephalitis, and brain abscess, diseases of quite different etiology, the changes in the spinal fluid are in many respects similar. Detailed examination of the fluid, especially when subsequent specimens are available, usually proves of reliable help in diagnosis. The various factors of value in differential diagnosis are:

Pressure.—The pressure is usually high normal or pathologically increased in all, and in tubercular meningitis tends to increase as the disease advances.

Cytology.—All characteristically produce lymphocytosis, but in the preparalytic stage of acute poliomyelitis and in rapidly advancing tubercular meningitis, polymorphonuclear leukocytes are present and may rarely outnumber the lymphocytes, a condition never seen in encephalitis and very rarely in abscess. The total number of cells is also of significance, 100 to 200 being found in poliomyelitis and tubercular meningitis; 20 to 40 in encephalitis and brain abscess.

Physical Characteristics.—The fluid in all these diseases may at first glance appear clear and colorless, but on close inspection is likely to be faintly *turbid* in tuberculous meningitis and perhaps in poliomyelitis. The most significant physical characteristic, however, is the formation of a fine, web-like clot of fibrin in the former disease. This is so constant that it should always be looked for when there is suspicion of tubercular meningitis. It forms best when the test-tube of fluid is gently placed on ice without agitation and allowed to stand over night; and appears suspended vertically in the fluid as a thread, which widens out at the surface of the fluid and forms the characteristic "pellicle."

Protein.—There is always an increase in the protein content, but as in the case of the cell count this is greater in poliomyelitis and tubercular meningitis (100 to 150 mgm. per 100 c.c.) than in encephalitis and brain abscess (40 to 80 mgm. per 100 c.c.).

Sugar.—Perhaps the most important single test is that for sugar, because early in the course of tubercular meningitis the sugar content of the fluid begins to fall (.04–.02 per cent.), while that of encephalitic fluids rises to high normal or pathological amounts (.07–.09 per cent.). Analysis of fluids from poliomyelitis and brain abscess usually show no marked variation from normal.

Bacteriology.—Investigators differ in their ability to find the *tubercle bacillus* in spinal fluid, and the presence of this organism is seldom demonstrated with ease. Two methods are advocated: to make films of the pellicle in which most of the cells and organisms are caught; and to add a protein precipitant, centrifugalize, and make films of the sediment. Organisms do not appear in the fluid in cases of encapsulated abscess. Search for the infectious virus of poliomyelitis and encephalitis is a task for the bacteriologist, with all of the equipment for inoculation and immunological research.

The *colloidal reactions* are positive in all of these diseases, but no characteristic or discriminative zones of reaction occur which can be employed in differential diagnosis.

The *Wassermann reaction* is negative in all.

By a careful evaluation of all of these tests it is usually possible to differentiate the four diseases. Especial emphasis should be laid upon the cytology (both the actual number of cells and the differential count), the protein content as shown by a quantitative method, the sugar content, and the search for tubercle bacilli.

3. Syphilis of the Central Nervous System.—Since the fluid varies with the type of neurosyphilis, and the stage and activity of the pathological process, it is necessary to consider separately the typical changes of the different clinical types of this protean disease in order to obtain a clean-cut conception.

Late Primary and Secondary Syphilis.—In late primary and secondary syphilis the fluid frequently contains a moderately increased number of lymphocytes (20 to 50), a slightly increased quantity of protein, and reacts positively in the Wassermann test. Occurring in so many patients during the efflorescent stage, most of whom never develop neurosyphilis, it is likely that the reaction often represents an aseptic meningitis, comparable with that described above. Still, some of the patients presenting this picture early continue to show positive fluid findings and do develop neurosyphilis, so that it is reasonable to consider these findings as consistent with incipient syphilis of the nervous system.

Acute Meningitic Syphilis.—During the first year, usually about six months after infection, acute meningitic symptoms may occasionally supervene. The condition of the fluid in such acute syphilitic meningitis is quite characteristic: the pressure is increased (250–350 mm.); the cell count is high (500–1000 cells), lymphocytes predominate, and polymorphonuclear leukocytes are numerous; the Wassermann reaction is strongly positive; and colloidal tests are positive, but variable in type. Fluid taken from patients with this acute meningitis has been shown, when inoculated into the testicle of a rabbit, to contain the *Treponema pallidum.*

Late Neurosyphilis—Active Stage.—While clinically late neurosyphilis may be separated into the tabetic, meningovascular, and general paretic types, it is impossible to do this by examination of the cerebrospinal fluid, although one specimen may show a "strong" and another a "weak" syphilitic reaction. The strong reaction is found almost without fail in general paresis, but is not pathognomonic, in that it occurs frequently in less severe manifestations of neurosyphilis.

The two types of fluid characteristic of late active neurosyphilis are contrasted in Table 1:

Table 1

	Strong Reaction.	*Weak Reaction.*
Cytology	10 to 40 mononuclears Plasma cells present	20 to 80 mononuclears Plasma cells rare
Total protein	80 to 125 mgm. per 100 c.c.	50 to 100 mgm. per 100 c.c.
Globulin ring test	Strongly positive	Weakly positive
Gold-sol	55554321000	1123321000
Colloidal benzoin	Strong	Weak
Wassermann	Strongly positive	Weak, moderate, or strongly positive
Blood Wassermann	Strongly positive	Positive or negative

Both series of tests unmistakably denote active neurosyphilis, but correlation with clinical experience suggests that the stronger reactions indicate more resistant infection and are associated with severe parenchymatous involvement. Such reactions are characteristic of general paresis, and in this disease are so constantly strong that a diagnosis of general paresis in their absence is questionable. Strongly positive reactions may also occur in fluid from patients with tabes and syphilitic optic atrophy. The weaker tests are characteristic of tabes and meningovascular syphilis when the process is active and advancing. In by far the larger number of progressive cases ot late neurosyphilis the reactions are of this character.

Late Neurosyphilis—Inactive Stage.—Many patients with obvious signs of neurosyphilis will be found to have normal or nearly normal spinal fluid. There may be a slight increase in the protein content and a weak gold-sol reaction, but no increase in the cell count and a negative Wassermann reaction. Such conditions are characteristic of an inactive stage of the disease, and usually indicate that the process is stationary whatever the extent of degeneration. Under successful antisyphilitic therapy a return of the fluid reactions to normal is to be expected, a drop in the cell count usually being the first sign of improvement, and followed by reduction of protein content and a change in the Wassermann reaction. The pathological gold-sol curve is often the most resistant abnormality. The fluid frequently, however, does not become completely normal, even in patients who show persistent clinical improvement. Under treatment the fluids of some patients remain "fixed," and sometimes react more strongly than before treatment. Experience shows that irrespective of apparent clinical improvement, such unaltered reactions indicate progress of the disease, and therefore a poor prognosis.

4. Spinal Subarachnoid Block.—Normally the spinal subarachnoid space contains fluid which is freely interchangeable within the spinal canal and subject throughout its length to variations in pressure. If at any point this space is constricted, two independent fluid chambers are formed. Change of pressure on one side of this block is not therefore transmitted to the other side (hydrodynamic evidence of block), and the composition of the fluid below the block also changes. The most conspicuous alteration is a marked increase in the protein content, presumably due to venous transudation (hydrostatic evidence of block). The most satisfactory although not the only method of demonstrating the hydrodynamic evidence of block is the artificial elevation of intracranial pressure by compression of the internal jugular veins of the neck. Normally the pressure rises promptly in the lumbar manometer; if block be present anywhere above the point of puncture, however, no elevation of pressure occurs. The hydrostatic evidence of block is readily seen in the marked increase in protein content, which below the block sometimes approaches that of blood-serum.

Two types of fluid have been described as characteristic of block: the one yellow, which clots on standing (Froin syndrome of *coagulation massive et de xanthochromie*), the other clear and colorless, which contains excess protein (Nonne syndrome). Neither type of fluid contains cells except in unusual cases when the block is associated with meningeal inflammation. It is quite probable that both represent different degrees of the same process. With both types of fluid block may be demonstrated by hydrodynamic tests.

Spinal subarachnoid block is caused by a considerable number of pathological processes, which may be classified according to location: (1) affections of the spine: tumors, abscesses pyogenic and tubercular, dislocations; (2) intraspinal, but extradural: epidural abscess, tumors; (3) intradural: tumors of the meninges, acute fibrinopurulent exudate, chronic adhesions, cysts; (4) intramedullary: tumors, gumma, syringomyelia rarely.

Complete Block.—Experience shows that, for the most part, colorless fluids, containing a large amount of protein and showing evidence of block (the Froin syndrome), occur especially in patients with pronounced transverse myelitic symptoms, in whom the level of block is well determined by clinical examination.

Incomplete Block.—There are, however, numerous patients from whom a colorless fluid is obtained, in which there is only moderate increase in protein content and no increase of the cell count (the cyto-albuminous dissociation of the French). In them a *partial block* may be demonstrated in a number of ways: by a slow rise in the manometric pressure following jugular compression; by the existence of a latent period before the rise following jugular compression; and by maintenance of a high pressure below the block after jugular release; or most commonly by a combination of these three methods. In such patients the diagnosis of block is less certain. Combined cisternal and lumbar puncture is advisable to permit comparison of the fluids above and below the block, which provides much more conclusive hydrostatic and hydrodynamic evidence than lumbar puncture alone. These tests of the permeability of the spinal subarachnoid space have been of very great service in the early differentiation of obstructive and compressive lesions of the spinal cord from spinal cord affections which are primarily degenerative and do not produce block.

In *tumors of the cauda equina* a fluid of high protein content, and frequently xanthochromic, may be found above the tumor. In such cases differential lumbar puncture should, when possible, be performed, with needles inserted above and below. Dynamic and chemical tests carried out in the same manner as in cases of cord tumor should lead to accurate localization of a caudal tumor.

5. Lateral Sinus Thrombosis.—A modification of the Queckenstedt test is applicable to the diagnosis of lateral sinus thrombosis. In such a condition compression of the jugular vein on the side of the lesion fails to elevate the fluid in the spinal manometer, whereas compression on the unaffected side causes an excessive elevation equivalent to that normally seen when both veins are compressed. The fluid findings are otherwise not characteristic, although they usually show evidence of mild aseptic meningitis. In the case of a mural thrombus this test is, of course, less striking.

6. Chronic Degenerative Diseases of the Central Nervous System.—In such diseases as progressive muscular atrophy, amyotrophic lateral sclerosis, and syringomyelia, no distinctive alterations of the spinal fluid have been found. As a rule, a slight to moderate increase in the protein content and the presence of an occasional lymphocyte and granular phagocyte give the impression that a destructive process is present; but the changes which we are able to demonstrate today are in no way pathognomonic.

In *active, progressive, multiple sclerosis* a combination of conditions is highly characteristic. With considerable uniformity the pressure of the

fluid is normal, the dynamic conditions normal, the protein content high normal or slightly increased (40 to 60 mgm. per 100 c.c.), a trace of globulin present, the cell count slightly increased (15 to 30 lymphocytes), and the Wassermann reaction negative. The colloidal reaction is, however, strong, and in the gold-sol test there is not infrequently a "paretic zone." While not pathognomonic, this combination of findings occurs often in multiple sclerosis and almost never in other diseases. It is, therefore, significant. In inactive, non-progressive, multiple sclerosis the fluid is normal or changed as in other degenerative diseases just described.

7. Cerebral Hemorrhage.—When bloody or blood-tinged fluid is obtained on lumbar puncture, immediate steps must be taken to determine whether the blood is in the fluid as the result of some abnormality or as the result of faulty technic. This point may usually be determined by receiving the fluid into three or more test-tubes, which will be decreasingly turbid if from the technic of puncture. If the fluid containing blood derived from a pathological source be centrifugalized, evidence of hemolysis will be seen in the supernatant fluid.

The fluid from a patient with recent cerebral hemorrhage is, therefore, uniformly bloody or blood-tinged. The supernatant fluid shows more or less red or yellow discoloration according to the age of the hemorrhage. The pressure is increased, at times markedly. The protein content is increased, but only moderately, even when the fluid is conspicuously blood-tinged; the increase is roughly proportional to the quantity of blood-serum in the fluid. An excess of white corpuscles is present because of the meningeal reaction evoked by the blood. When the hemorrhage is of a week's standing, the pressure may be normal and the fluid yellow and translucent. Microscopically the corpuscles appear swollen and colorless. After two weeks the fluid has usually become normal or nearly so. There is nothing which differentiates the bloody fluid of spontaneous cerebral hemorrhage from that of trauma.

Extradural bleeding, usually from rupture of the middle meningeal artery, is a form of intracranial hemorrhage which causes no blood to enter the spinal fluid, but produces excessive and increasing pressure. This is of prime diagnostic significance.

8. Communicating Hydrocephalus and Serous Meningitis.—The outstanding features of communicating hydrocephalus and serous meningitis are the presence of an excessive amount of spinal fluid and a diminished concentration of the fluid. The excessive amount of fluid (50–75 c.c.) may be estimated by measuring the amount obtainable (normally about 15 20 c.c.) with the patient in the lateral position. An idea of the quantity may be obtained also by noting the rapidity of drop in pressure on withdrawal of known amounts. Normally the pressure drops approximately 50 mm. in the manometer after withdrawal of 10 c.c. When the quantity is large the drop is much less, perhaps 10 or 20 mm. The lowered concentration of the fluid is best demonstrated by the protein tests; these may show almost no turbidity, not infrequently so little that it cannot be accurately measured.

9. Uremia and Diabetes.—In at least two diseases in which metabolism is markedly altered there are characteristic changes in the spinal fluid. In uremia the non-protein nitrogen content is elevated and in diabetes the sugar content is increased. This increase is roughly in proportion to

but never as great as that in the blood. In nephritis, and especially in uremia, the pressure is likely to be high and the amount of fluid increased. If vascular accidents have occurred the total protein content is also increased.

10. Brain Tumor.—Lumbar puncture in the presence of subtentorial tumor should be considered a dangerous procedure and should not be performed, except as indicated below. Lumbar puncture in patients with tumors above the tentorium is usually safe, but frequently aggravates the symptoms, and is, therefore, not to be performed without consideration. It is probable that any physician who has had wide experience with lumbar puncture has had personal experience with or knowledge of death, either immediate or within twenty-four hours, following withdrawal of fluid. Usually the cause is a tumor in the cerebellar fossa, which produces hydrostatic pressure and medullary paralysis by wedging the medulla in the foramen magnum.

When it seems essential to examine the spinal fluid, although a tumor may be present it is reasonably safe to tap the spine if there is no well-marked elevation of the optic disks. If the disks are choked, however, it is wiser to omit lumbar puncture entirely, or perform combined ventricular-lumbar punctures, which provide more valuable information and are safer. By this method the lateral ventricle is tapped first and the pressure lowered before lumbar puncture is performed. Then manometers are attached and dynamic studies carried out as in the case of suspected spinal subarachnoid block. With subtentorial tumor a partial ventriculo-subarachnoid block is characteristic; tumors above the tentorium produce no evidence of block.

Pressure in the case of tumors varies greatly, from high normal to the highest recorded in any disease (frequently 700 to 800 mm.), depending on the size and situation of the tumor. A pressure of 1000 mm. has been reported.

The protein content of the fluid also varies. It is most often just above normal (50–60 mgm.), but may reach 100 to 200 mgm. per 100 c.c., especially with subtentorial tumors. In such patients there is a sharp contrast with the low protein content of the ventricular fluid, and dynamic evidence of block is of prime importance in localization.

It would seem that the quantity of albumin is increased rather than that of globulin, although quantitative tests for the latter are not yet satisfactory. This is a minor point in the differential diagnosis of tumor and syphilis.

Often no cells are found. More frequently a few arachnoid cells and lymphocytes give evidence of local irritation.

There is usually an abnormal reaction in all colloidal tests, but there is certainly no distinctive zone in the benzoin, mastic, or gold-sol reaction.

The Wassermann reaction is said to be occasionally positive with tumor, but it is usually negative. An unrecognized, associated, syphilitic process is a reasonable explanation for this rare anomaly.

Significance of Normal Fluid Findings.—The above groups represent the chief pathological conditions in which positive findings are of proved value in differential diagnosis. Hardly a year passes but that another disease or physiological disorder is added to the list as showing characteristic changes in the spinal fluid, sometimes of prime importance.

Only less valuable is the finding of normal fluid in excluding diseases which regularly are known to produce typical changes.

Like all laboratory tests, those of the cerebrospinal fluid must be closely correlated with the clinical picture. Seldom can the laboratory worker alone make the diagnosis, although analysis of all the tests of proved value will further our knowledge of many an obscure neurological puzzle.

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SYPHILIS OF THE CENTRAL NERVOUS SYSTEM

MENINGOVASCULAR, TABETIC, AND PARETIC NEUROSYPHILIS. CONGENITAL NEUROSYPHILIS

"Neurosyphilis" is a general term which includes all those disorders of the nervous structures, the envelopes surrounding them, and the blood-vessels traversing them which are caused by the *Spirochæta pallida*. The organism usually invades the nervous system early in the course of syphilis, although symptoms may not appear for many years. The symptoms may be of almost any variety, but may logically be considered as variations of a common disease caused by a single type of organism. The clinical manifestations depend on the localization of the virus and the pathological changes, which, in turn, depend on the inherent reaction of the tissue invaded. In 1913, when the *Spirochæta pallida* was found in patients with general paresis and tabes dorsalis, evidence that these syndromes are types of neurosyphilis seemed to be complete. At the same time the concept of parasyphilis lost much of its meaning, and with more satisfactory methods of treatment it is no longer necessary to consider it.

The brain and spinal cord are composed of neurons and neuroglia cells. Both are formed from the ectodermal layer. The neurones are formed from the true parenchymatous tissue. The meninges and blood-vessels are derived from the mesoderm and are in no sense true nerve tissue, but because of their close anatomical relationship with the brain and spinal cord, any pathological changes in them directly influence these latter structures. From the viewpoint of morbid anatomy, clinical symptomatology, and response to antisyphilitic therapy it is convenient to think of neurosyphilis as being predominantly meningeal, vascular, or parenchymatous. Such is the basis of the following discussion.

Etiology.—The *Spirochæta pallida* is the cause of all neurosyphilis. While the disease is generalized (primary and early secondary period) and the entire body is being invaded by the spirochetes, the central nervous system rarely escapes. This is evidenced by the symptoms, the serological changes, and the presence of the spirochete in the cerebrospinal fluid. In many cases the central nervous system apparently becomes sterilized and undergoes no later change, but in 30 to 40 per cent. this reaction of immunity

is lacking or only partial, and the spirochetes remain present within the central nervous system only to produce symptoms in later months or years. Why some infected patients develop active neurosyphilis and the majority escape has been explained in several ways, but no explanation is scientifically proved or free from doubt. For example, it has been stated that the incidence of neurosyphilis depends on the constitution and heredity of the individual affected; and studies have been made which purport to show that neurosyphilitics are of the neurotic type. Bolton claims that the histological brain pattern which permits general paresis to develop can be recognized. The theory that a particular strain of spirochetes has a definite neurotropism has also been advanced by numerous observers: and there are several famous instances of the development of paresis or tabes in different individuals infected from the same source. Conjugal neurosyphilis is relatively frequent. Experimental evidence that there is a difference in the reaction of spirochetes taken from the fresh chancre and from the brain of the paretic has been obtained by Levaditi and A. Marie. Their evidence, however, is not free from criticism. Another theory is that the condition of the patient at the time of his infection and the character of his immunity responses are all of primary importance. This latter view seems to be the best at the present time, if only because it leads to thorough investigation of the nervous system in every syphilitic patient, regardless of the stage of the disease.

Symptoms.—The symptoms characteristic of early neurosyphilis of all types are headache, due usually to the meningitis, vertigo, blurring of vision, and mild optic neuritis. None are necessarily present. The spinal fluid during the primary and early secondary period frequently undergoes mild changes. Its lymphocytic content increases, globulin is present, the gold-sol reaction changes, and the Wassermann reaction may be positive. All these abnormalities may occur together. At times the Wassermann reaction of the spinal fluid is positive before that of the blood becomes positive. Spirochetes which could be grown in animals have been recovered from the spinal fluid in the very earliest stages of the disease. As a rule the symptoms disappear, either with treatment or spontaneously, in much the same manner as does the skin roseola, a fact probably to be accounted for by the immunity which the patient develops.

Types.—Meningovascular Neurosyphilis (*Cerebral Syphilis, Spinal Syphilis, Cerebrospinal Syphilis, Syphilitic Meningitis, Cerebral Gumma*, etc.).—*Definition.*—Meningovascular neurosyphilis is an involvement of the membranes or vessels of the nervous system by the *Spirochæta pallida*, with or without secondary involvement of the nervous parenchyma.

Incidence.—The condition is said to develop usually within the first five or six years after infection, and is associated with congenital as well as with acquired syphilis. No very definite statement can be made about the incidence of the various types of meningovascular neurosyphilis, but it may be stated that approximately 20 to 30 per cent. of all patients with syphilis develop meningovascular symptoms.

Morbid Anatomy.—In the vast majority of cases the primary pathological changes occur in the meninges and blood-vessels, and are, therefore, similar to the syphilitic lesions in other mesenchymal tissues. In the *meninges* the reaction is of an exudative nature, and the tissue is invaded by inflammatory cells, for the most part by small lymphocytes, but also by a few large

lymphocytes and endothelial cells and an occasional plasma cell. The lesion is chiefly in the pia arachnoid, although at times the dura is also involved. In the very acute fulminating condition, which is quite rare, polymorphonuclear leukocytes may make up 50 per cent. of the infiltrating cells. The meningitis may be somewhat localized, or so extremely diffuse as to affect all the cerebrospinal meninges. In the mild type the infiltration is only slight, but it may become extremely marked. The macroscopical picture of the pia of mildly affected patients is almost normal, a slight haziness being the only visible change. If the lesion is more marked, the membranes may be greatly thickened, have a matted appearance, and occasionally even resemble creamy pus. The very large gummatous lesions which may develop are similar to the gummatous tumors seen in other parts of the body. Although the most frequent site of the meningitis is the base of the brain and the thoracic portion of the spinal cord, other parts of the meninges may also be involved. Individual nerve-fibers may be surrounded by the exudate and compressed; and when the basal meningitis is relatively severe, several nerves may be affected. At times the spinal meningitis is so intense that the circumference of the cord is greatly compressed, with consequent degeneration of the fiber tracts.

Cerebral irritation with secondary response may result from meningitis of the convexity. Optic neuritis sometimes follows invasion of the pia in the region of the optic chiasm. In certain acute conditions the cerebral cortex is involved by extension, the spirochetes invading the cortical tissue, and causing an encephalitic complication.

The lesions of the cerebral *blood-vessels* are similar to the vascular changes in other parts of the body, the perivascular sheaths being infiltrated with lymphocytes. There is some question whether the process starts in the intima, media, or adventitia, but it is probable that the media undergoes the first change. The relation of the coats becomes altered, and because the elastica splits and the intimal lining is broken, thrombi frequently form. This is the most common serious vascular accident of neurosyphilis, although at times hemorrhages occur from the weakened vessels.

From the lesions of the more acute types of meningitis and meningoencephalitis, the spirochetes are relatively easily obtained; from those of the chronic type and from gummata, on the other hand, very few can be isolated.

Symptoms.—The symptoms of meningovascular neurosyphilis vary greatly according to the location and extent of the lesion, the relative severity of the meningeal and vascular changes, and the extent of the pathological process. That meningovascular neurosyphilis may simulate any form of nervous or mental disorder and produce symptoms resembling those of any neuropsychiatric condition should always be kept in mind.

Although symptoms may develop within the very earliest period of the syphilitic infection or not appear until forty years or more after the primary stage, certain manifestations have come to be associated with the different stages of the disease. In the first weeks of the syphilitic infection the symptoms of cerebrospinal involvement are usually quite mild, and consist chiefly of headache (probably due to meningeal irritation), tinnitus aurium, vertigo, and blurring of vision. At times pains may be caused throughout the body by irritation of the spinal nerves. Ophthalmoscopic examination frequently reveals papillitis. During this period, however,

there may be symptoms of a very severe cerebrospinal meningitis, with intense headache, rigidity of the neck, Kernig sign, and complete prostration. Such a syndrome requires prompt and vigorous antiluetic treatment.

In the period beginning six months to a year after the primary stage severe meningovascular disasters, including meningo-encephalitis, occur with relative frequency. The meningitis may be either cerebral or spinal. A palsy of one or more of the cerebral nerves may develop, which is fleeting and disappears within a few days or may be more permanent. When it is of very short duration recurrences are frequent. Headache, dizziness, and visual and auditory symptoms are often noted. Spinal cord symptoms are less frequent, but may develop as "rheumatic" pains in any part of the body, and occasionally as disturbances of the sphincters. Very marked spinal meningitis at the dorsal level sometimes leads to compression of the cord, or to so-called transverse myelitis with resulting spastic paraplegia. Erb considered the syphilitic spastic paraplegia which bears his name as a primary degeneration of the corticospinal tracts, but it is doubtful if such an entity exists, because the few cases that have been studied pathologically show compression of the cord by the meningitis. Gummata are quite infrequent in the first year.

The *vascular disorders* are the most dreaded complication of the early period. Thrombosis of one of the large meningeal or cerebral vessels is not infrequent. The Sylvian and lenticulostriate arteries are particularly susceptible to this lesion; this results in hemiplegia. These apoplectic conditions often come on without warning, or, on the contrary, the patient may awake after a few days of headache and dizziness to find himself paralyzed. The paralysis is the result of a destruction of brain tissue, due to the shutting off of the blood-supply. Although this condition usually develops during the first five to seven years after infection, the syphilitic patient is liable to such manifestations of meningovascular syphilis throughout life.

Serology.—During the primary and early secondary period of mild neurosyphilis the changes in the spinal fluid are relatively insignificant. Occasionally the Wassermann reaction is positive, but more frequently there is slight pleocytosis (10 to 25 cells per cmm.). A little globulin may be present, and there may be a weak gold-sol reaction. The blood Wassermann is negative during the early part and positive during the later part of the primary period. In the early secondary period of very mild cases the spinal fluid is very similar to that found during the primary stage, while the Wassermann reaction of the blood is usually positive.

In patients with symptoms, the reactions of the spinal fluid are likely to be rather strong after a few months. In most instances the Wassermann reaction is positive with 1 c.c. of fluid. The cell count may be quite high (20 to 200 cells per cmm.), and when the meningitic symptoms are relatively severe, may run up into the thousands. The fluid nearly always contains globulin and an increased quantity of albumin. The gold reaction usually follows the so-called luetic curve. At times the serological reactions may be strongly positive, and resemble those of paretic neurosyphilis.

If the lesions are chiefly vascular the serological findings may be the same as those of the meningeal form, but often they approach normal.

Prognosis.—Although the prognosis of meningovascular neurosyphilis is

better than that of any of the other types of the disease, no general statement can be made, because there are so many different manifestations of the condition, and the changes vary so greatly in the different stages. The outlook for patients with meningeal lesions, whether early or advanced, is usually excellent if treatment be adequate. For those with fulminating neurosyphilis, it is very doubtful even with the best of treatment; and if adequate and active therapy be omitted, the prognosis is hopeless. Of the strictly vascular conditions there are two types: one which becomes manifest at an early period and may be so arrested by suitable treatment that there are no further vascular changes; and another which appears at a later stage and responds to therapy less satisfactorily because the vascular lesions are more generalized. Most patients however, do, improve greatly after treatment.

Tabetic Neurosyphilis (*Tabes Dorsalis, Locomotor Ataxia, Syphilitic Posterior Spinal Sclerosis*).—*Definition.*—Tabetic neurosyphilis is an infection characterized by visceral crises, and symptoms referable to the afferent spinal nerves and the nerves of special sense. The kinesthetic and pain fibers are, as a rule, first affected; this leads to progressive loss of position sense and to lancinating pains. Trophic disturbances and disorders of the cerebral nerves are also frequently associated with the condition.

Morbid Anatomy.—There is a degeneration of the posterior columns of the cord, of the posterior roots, and, to some extent, of the posterior ganglia. Sometimes the optic nerve degenerates, and at other times the sensory nerves may be involved. Meningitis, generally of a mild chronic type, usually accompanies tabes dorsalis.

Pathogenesis.—There is a general belief that the pathological changes in tabes originate in the intradural portion of the posterior root. The French school has called attention to the possibility that the lesion may start in the posterior ganglia. The degeneration of the cells of these ganglia is, however, rarely sufficient to explain the degree of degeneration within the posterior root. Much notice has also been given to the idea that a toxin circulating in the spinal fluid affects the posterior root; but this theory has been rendered less acceptable by the more modern conception that all the morbid changes of neurosyphilis are caused by activity of the spirochetes rather than by their toxin. The fact that meningitis practically always develops has evoked the suggestion that the posterior root is pinched in the inflammatory process (compare with cerebral nerve palsies due to basal meningitis), but this does not explain the relatively infrequent involvement of the anterior roots.

The recent work of Richter seems to demonstrate that the tabetic lesion is due to activity of the spirochete itself and that the local change consists of a specific granuloma in the posterior root. Richter has apparently succeeded in his attempt to show that the meningitis is a secondary and not a primary tabetic lesion; or, in other words, that tabes may exist without meningitis. The anatomical relationship, as first pointed out by Nageotte, is such that there is a more acute angle made by the posterior root and the meninges than by the anterior root. According to Richter, this offers a recess with less fluid in circulation in which the spirochetes can locate, and this accounts for the greater frequency of involvement of the posterior than of the anterior root. He points out, however, that the latter is affected late in the disease. He has been able to demonstrate the

presence of spirochetes in what he describes as a definitely specific granuloma of the posterior root. This theory seems to be the most satisfactory and coincides most nearly with the present concept of the parasitology of syphilis.

Symptoms and Signs.—Most of the typical signs and symptoms of tabetic neurosyphilis appear only after the disease has persisted for some time, and relatively few develop during the very early stages or in atypical conditions. In the early stages tabes may be of two types: in one, the symptoms develop before the neurological signs; in the other, the signs are the first to appear. In fact, in one group of patients the neurological findings may be very nearly normal, while there are such typical symptoms as lancinating (rheumatic) pains, gastric crises, and other visceral crises. The diagnosis is confirmed by the spinal fluid findings. In another group, Argyll Robertson pupils and the absence of the tendon reflexes may be obvious before any symptoms develop.

Of the characteristic *symptoms*, the most common are related to the sensory system and are apparently caused by pathological change in the posterior roots. These symptoms are of the type of painful sensations or kinesthetic abnormalities, the latter of which lead to motor inco-ordination. Such visceral symptoms as gastric, rectal and other crises, and disorders of the sphincters are also characteristic, as well as those related to the special senses (blindness as the result of atrophy of the optic nerve, and deafness). Trophic changes (perforating ulcer and Charcot joint) also occur.

Pain, which is the most common of the early symptoms, usually begins in the legs, and sooner or later becomes very severe. It is often described as a burning, gnawing, or lancinating sensation, such as might be produced if a hot knife were stuck into the flesh and twisted. The attacks which come on with lightning-like rapidity last for hours, and are followed by only a brief interval of freedom. Such attacks may recur throughout many years. In some instances there is a sensation of constriction about the waist or chest (girdle sensation), which follows involvement of the radicular nerves. Associated with the attacks are all sorts of abnormal sensory phenomena, such as paresthesia, numbness, severe pains, and sensations of cold, warmth, or tingling. When the pain is very severe pressure on the skin may give relief, or be intolerable because of the exquisite sensitiveness. Occasionally ecchymoses appear on the skin in the region where the pain is felt.

Ataxia (inco-ordination), the result of loss of the fibers of the posterior roots and posterior columns, often appears after the onset of the pain, although it may be the earliest symptom and be unassociated with any other disorder of sensation. It usually involves the lower extremities, but occasionally affects the hands when the cord lesions are cervical. The change of gait, which usually develops slowly, is ordinarily first noticed when the patient is walking in the dark. Once in a while the change comes very suddenly. The abnormality varies from a slight unsteadiness in the early stages to a marked change of gait in the late stages in which the foot is thrown into the air and brought down unsteadily as if being slapped on the floor. This latter condition is characteristically tabetic.

During the early stages there is little if any loss of the tactile, pain, or temperature *senses*. Hypesthesia and hypalgesia develop later. Hyperesthesia, especially of radicular distribution, is quite common. Rarely,

in the late stages, complete anesthesia develops and is followed by disappearance of the pain, which may have been very severe. The loss of kinesthetic sense as shown by inability to feel passive movements of the toes or fingers may be noted quite early.

The *visceral crises* are relatively common manifestations. The mechanism of their production is not known. That most frequently seen is the *gastric crisis*, which is characterized by recurrent abdominal distress and vomiting, often associated with considerable pain in the abdomen. The attacks come on without relation to food, and may persist for hours or days at a time. After the crisis has passed the patient feels well and has no gastro-intestinal symptoms. The attack may be extremely severe and controlled only by large doses of morphin. The character of the crisis varies greatly. Some patients have mild nausea and distress, while others vomit almost daily. This manifestation is not related to the general function of the gastro-intestinal tract, and gastric analyses and *x*-ray studies are entirely negative in the typical uncomplicated case. Since in some patients, gastric crises are accompanied by no other troublesome tabetic symptoms and the reflexes may be quite normal, some authorities consider the gastric crisis a separate syndrome.

Crises of other organs also occur. Those in the rectum are characterized by diarrhea or tenesmus; those in the larynx by local spasm.

Disorders of the sphincters are at times the first symptoms. The common difficulty in voiding urine is followed, or occasionally preceded, by incontinence. In relatively few cases there is also loss of control of the rectal sphincter. Loss of sexual power is a frequent and often an early symptom.

Atrophy of the Nerves of Special Sense.—Mild *optic atrophy* occurs in many cases of tabes; that leading to marked diminution of vision or complete blindness, however, develops in about 10 per cent. of all tabetic patients, and may be an early or almost isolated symptom. Like gastric tabes, it may occur without the usual cord signs and symptoms, and is often designated as optic tabes. The *auditory nerve* is sometimes similarly involved, but marked degeneration is less frequent. Symptoms depending upon atrophy of the *other nerves of special sense* are rare.

Although *trophic disturbances* usually appear during the very late stages, *Charcot joints* may develop at any period. *Perforating ulcers*, which were formerly seen quite frequently, are now extremely rare, possibly because of modern methods of treatment.

The most important *neurological signs* are: (1) absence of the knee-jerks and ankle-jerks, and less frequently of the tendon-jerks of the upper extremities; (2) the Romberg sign (inability to stand with the feet approximated and the eyes closed); (3) ataxia of the legs and less often of the hands; (4) pupillary changes, irregularity, inequality, sluggishness, and the typical Argyll Robertson condition; (5) loss of control of the sphincters and sexual impotence; (6) sensory disturbances such as hypesthesia and even anesthesia; and (7) Charcot joints.

The *tendon reflexes* are typically lost early, frequently before the appearance of any symptoms. Their absence is caused by interruption of the reflex arc when the fibers of the posterior roots are destroyed. Those of the lower extremities often disappear while the reflexes of the upper extremities are retained, although when the upper part of the cord is involved

the reverse is true. The ankle-jerks are frequently lost before the knee-jerks. In many cases of tabes the reflexes are retained, especially when there is evidence of gastric crises or optic tabes. The *skin reflexes* may be present or absent. The *abdominal reflexes* are likely to be absent, because they are frequently lost in syphilitic patients. The *cremasteric reflexes* persist, except in unusual or advanced conditions.

The noteworthy *Romberg sign* may be observed before the patient has noticed any difficulty in walking.

Pupillary Signs.—As in other types of neurosyphilis, irregularity and inequality of the pupils is a common early sign. The pupils are almost always unequal, and their early sluggishness of response usually increases until they are of the typical Argyll Robertson type, *i. e.*, respond to accommodation but not to light. This type of reaction is seen more commonly in tabes than in any other form of neurosyphilis. The pupils may be so contracted that their diameter is less than that of a small pin-head, but they may also be quite large. In not a few cases they become fixed and react to neither light nor accommodation.

Motor Palsies.—Paralysis of the extrinsic eye muscles, especially the levator palpebræ and the external or internal recti, may be the first manifestation of tabetic neurosyphilis to attract the patient's attention. Such palsies may occur years before any of the other characteristic symptoms of tabes. They are usually temporary, lasting for a few days or weeks, but are sometimes permanent. As a rule, they are accompanied by reflex anomalies in other parts of the body which are revealed by examination. Lid-drop or diplopia often precedes by several years the symptoms of which a tabetic patient complains, but since these conditions right themselves rather promptly they are often not seriously considered.

In the late stages of the disease the intrinsic muscles of the hand or foot may become wasted and also, although more rarely, the larger muscles. This may result from degeneration of the anterior horn-cells, pinching of the anterior root by the meninges, or, as Richter suggests, from degeneration of the anterior root caused by spirochetal action at the junction of the anterior and posterior roots.

Serology.—Probably in the tabetic type, as well as in the other forms of neurosyphilis, changes take place in the spinal fluid before either signs or symptoms of the disease become manifest. The reactions of the blood and spinal fluid in tabetic neurosyphilis are very similar to those in the meningovascular type. Not infrequently the spinal fluid resembles that recovered from paretic patients; and occasionally it is entirely negative, apparently because of spontaneous arrest, a condition which leads to the concept of a burned-out process.

Diagnosis.—Serological tests usually permit recognition of tabetic neurosyphilis before the appearance of marked symptoms and signs. Consequently, when laboratory methods of diagnosis are employed and modern treatment is promptly instituted, fewer cases are allowed to assume the typical characteristics. It is well to bear in mind that a typical case is relatively far advanced and is past the stage in which the clinician can take pride in making a diagnosis.

Prognosis.—Without treatment the symptoms usually increase slowly for many years, until the patient finally becomes bedridden. Frequently, however, the progress is so very slow that the change from year to year is

only slight. Symptoms, at times, develop very rapidly and often cease spontaneously.

Paretic Neurosyphilis (*General Paresis, General Paralysis, General Paralysis of the Insane, Dementia Paralytica*).—*Definition.*—Paretic neurosyphilis is a chronic syphilitic meningo-encephalitis, characterized by progressive dementia and a diffuse, generalized paralysis which terminates in death.

Incidence.—About 3 per cent. of syphilitic patients develop symptoms of paresis. They occur approximately five or six times as frequently in men as in women, although the incidence of luetic infection is not so greatly different in the two sexes.

Morbid Anatomy.—In paretic neurosyphilis there is, characteristically, a macroscopical thickening of the dura, which is frequently adherent to the calvarium. Pachymeningitis hemorrhagica is occasionally present. The pia-arachnoid becomes more or less thickened, especially over the frontal regions, and is usually milky or translucent. Frequently, cerebrospinal fluid accumulates between the pia and the cortex as a result of cerebral atrophy. This cerebral atrophy is most prominent at the frontal poles where the lesions are most marked, and is manifested by widening of the sulci and flattening of the convolutions. The ventricles are usually enlarged and ependymitis or roughening of the fourth ventricle is usually visible.

Microscopically, the disease is characterized by degeneration of the nerve-cells, especially in the frontal region, and as the disease progresses, or in aberrant types, in any part of the cortex, cerebellum, and bulb. The structure of the cortex is greatly disturbed. All types of pyknotic changes are present. Completely degenerated cells are in close proximity to well-preserved cells. Gliosis compensates in part for the loss of nerve elements. Satellitosis and phagocytosis occur, and rod cells are often present. Perivascular infiltration of the small vessels of the cortex, white matter, and pia with lymphoid cells is always present. Most striking and most characteristic is the presence in the tissue of plasma cells, which in some instances form the majority of the infiltrating cells. It is usually said that new blood-vessels form in the affected areas. Vascular sclerosis of the larger vessels is not a part of the paretic process and is to be considered a complication. Degeneration of the fibers of the projection system results from the neuronal loss, so that in late cases there is often degeneration of the corticospinal tract. Tabetiform lesions of the cord are common.

Symptoms.—The symptoms of paretic neurosyphilis are protean in character and form almost any syndrome. The onset is at times insidious, at other times sudden. For systematic discussion the mental symptoms may be divided into three groups: (1) those of the period of onset, often spoken of as the "medico-legal state"; (2) those of the period of full development of the disease; and (3) those of the terminal period in which the patient is bedridden. Such a division is entirely arbitrary and in many cases impracticable. A galloping form of the disease is described which progresses very rapidly, and leads to death within a short period.

1. *The Early Stage.*—Any *change in the personality of an adult* should arouse suspicion of paretic neurosyphilis. The first change in character may be very slight and of brief duration, a slight change in manner, for instance, greater irritability, carelessness about the clothes and person,

lack of judgment, absent-mindedness, inability to concentrate, increased fatigability, hypersuggestibility, and slowness of comprehension. These symptoms may develop very early and be of very little apparent significance in themselves. They may, however, lead to such disasters as heavy losses in business, alcoholism, and loss of reputation because of various excesses. Very frequently *neurasthenic symptoms* develop, or, on the other hand, mild depression or euphoria and elation. These symptoms may become much more marked after a period of days, weeks, months, or even years, and lead to symptoms characteristic of the well-established phase of the disease.

The early physical signs and symptoms include headache, visual disorders, and diminished acuity of smell or hearing. Often there is a slight disturbance of manual dexterity, *i. e.*, tremors of the outstretched hands and inability to make co-ordinated movements. The frequent decrease of muscle tone, especially of the face, results in flattening of the nasolabial folds which reduces the facial expression and markings and often makes the patient appear younger than he is. Another characteristic symptom is a speech defect which causes poor enunciation of such test phrases as "Methodist Episcopal," "third riding artillery brigade," etc.

The *pupillary changes* of neurosyphilis appear in the paretic form as in all others. The typical Argyll Robertson pupil can only infrequently be seen. In the early stage, the reaction of the pupils may be quite normal or the dilated pupil may respond poorly to light. Later there is no reaction to light, but there is response to accommodation, and finally both types of reaction are lost.

Changes in the *tendon reflexes* are common. Atrophy of the efferent or afferent pathways may not be so balanced as to alter the reflexes, or may increase, diminish, or destroy them. As a rule, the changes of the tendon reflexes are relatively late manifestations, although they may take place before the onset of any other recognizable symptoms. The Babinski sign, ankle clonus, and other pathological reflexes are to be observed in the early stage, but are usually associated with atypical conditions or vascular complications; late in the disease they are common. In the early stages the sphincters are rarely involved and there is often increased sexual potency.

Sometimes the period of onset is short, and the disease attains the fully developed stage with great rapidity; in fact, a seizure may occur in a person in apparently good mental and physical condition and be followed by well-developed symptoms of the established stage. The progress may, however, be so slow that a year or more elapses between the onset of mental symptoms and the development of the characteristic syndrome.

2. The *stage of full development* is characterized by varied symptoms which may mimic any type of mental disease. Typically, there is *euphoria*, and the patient is grandiose, elated with delusions of wealth and great prowess, and feels better than ever before. This classic syndrome appears in only 10 to 20 per cent. of cases. Another type is that of *depression*, with anxiety, fear of impending danger, and self-accusation. A third well-recognized syndrome is that of a *simple dementia*, in which, without either excitement, depression, or delusion formation, the mind of the patient deteriorates. In a fourth form *paranoid ideas* predominate. There are many other variations which need not be mentioned here.

Common to all the forms and of the greatest importance is the *progressive dementia.* Loss of memory, especially for recent events, later for past events as well, difficulty in calculation and writing, the elision of letters, and defects of judgment are sooner or later apparent.

Paretic seizures of either the epileptiform or apoplectiform type, which are frequently accompanied by transient paralyses, are characteristic of this stage. The defect of speech is more marked, and the disorders of the reflexes become quite prominent.

3. *Terminal Stage.*—In the third stage physical weakness becomes very great. The patient becomes bedridden, and finally reaches the condition of a vegetative organism. There is emaciation, bed-sores develop, and generalized paralysis of all the muscles of the body ensues. If death is not caused by a seizure or by intercurrent disease, it finally results from paralysis of the respiratory muscles.

Prognosis.—Paretic neurosyphilis has in the past been considered invariably fatal, but at the present time some modification of this idea is possible because of various new forms of therapy. Untreated patients, who still are far more numerous than those who receive adequate treatment, live on the average two and a half to three years after the onset of definite symptoms. Some patients, however, die in a seizure at the very onset of the disease; others linger for five to six years; and, very exceptionally, a patient lives as long as nine or ten years.

Spontaneous remissions are characterized by improvement of both the mentality and the physical condition of the patient. This may be so great as to allow the patient to return to his former occupation. These remissions usually last no longer than six months; very rarely they continue for a year. In a few cases they have been reported to persist for a period of years. Spontaneous remissions occur in 2 to 10 per cent. of patients.

Syphilitic Spinal Muscular Atrophy.—A quite rare form of neurosyphilis is that in which degeneration of the anterior horn cells of the spinal cord produces the syndrome of progressive spinal muscular atrophy. The lesion consists of perivascular infiltration with lymphocytes and plasma cells, and meningitis similar to that of tabes, associated with atrophy of the anterior horn-cells. The clinical diagnosis depends on the neurological signs of neurosyphilis and the changes in the spinal fluid.

Syphilitic epilepsy is not a well-defined syndrome and there is much discussion concerning its existence. *Three types* are described: in the first, though there is no pathological or serological evidence of neurosyphilis, epileptic seizures develop some time after the syphilitic infection of an individual supposedly without hereditary epileptic taint who has never had previous convulsions; the second type is supposed to be related to meningovascular neurosyphilis and is apparently the result of irritation of the brain; in the third type there is a parenchymatous disorder of luetic origin. In the two latter there is the suggestion of an etiological connection between the convulsions and syphilis; in the first such an hypothesis has little foundation. It is true that epileptiform seizures are not rare in all types of cerebral neurosyphilis, but the recurrence of convulsions over a period of years is very uncommon.

Antisyphilitic treatment has not been sufficiently successful to demonstrate satisfactorily the existence of a true syphilitic or neurosyphilitic epilepsy.

Syphilitic paranoia is described in the German text-books as a condition in which the patient has the clinical evidences of paranoia in conjunction with syphilis or neurosyphilis. It is even less well established than the syphilitic epilepsies.

Syphilis of the peripheral nerves may be secondary to disease of such nearby structures as bones, fasciæ, and muscles. Gummata may encroach upon and implicate the nerves. The peripheral nerves may, however, be affected by a direct extension of the inflammatory reaction along the lymph-channels and perivascular spaces. Such neuritis is known to cause palsy of motor nerves or, in the case of the sensory nerves, neuritic pains.

Congenital neurosyphilis closely simulates all the syndromes of acquired neurosyphilis. Only too frequently the nervous involvement in congenital syphilis is not recognized during the early years of the patient's life. Recent studies have shown that about 20 per cent. of the patients with congenital syphilis show clinical or serological evidence of neurosyphilis. Symptoms may make their appearance in the first years of life; or may be delayed until adolescence, when they suggest meningovascular, tabetic, or paretic neurosyphilis.

Juvenile tabetic neurosyphilis is very unusual. The symptoms are quite similar to those of the acquired form, except that pains are perhaps less frequent.

Juvenile paresis is relatively very frequent as compared with juvenile tabes (50 : 1 in the author's series). The usual age of onset is between twelve and eighteen years. The patient may have appeared to be quite normal before the paretic symptoms develop, showing few, if any, stigmata of congenital syphilis. The characteristic clinical manifestation is usually dementia which progresses rather rapidly. Occasionally the symptoms are those of grandiosity. In other instances the child fails to develop mentally, and is considered feeble-minded. The duration of life is usually from three to five years after the onset of mental symptoms.

The serology of all juvenile neurosyphilis is identical with that of the acquired form.

Syphilitic feeble-mindedness is described in many text-books, but the author has not recognized such an entity. Unless there is definite luetic involvement of the brain, the juvenile syphilitic usually has the mentality characteristic of his family.

Diagnosis.—As the various syndromes of neurosyphilis simulate almost any organic or functional disease of the nervous system, it is necessary to consider the possibility of the disease whenever neuropsychiatric signs or symptoms develop. The history of syphilis and examination of the blood and spinal fluid usually suffice for diagnosis of neurosyphilis. It is unusual and rare for the serology to be negative. Frequently it is only by examination of the spinal fluid that diagnosis is possible. When the serology is negative, the diagnosis of neurosyphilis is permissible only if the symptoms are very characteristic, since experience has shown that such conditions are usually non-syphilitic. It is nearly always advisable to confirm the clinical diagnosis by examination of the spinal fluid.

Differentiation of the various forms of neurosyphilis is made by the symptoms and to some extent by the condition of the cerebrospinal fluid. Even pathologically, however, it is not possible to distinguish all types.

Thus, syphilitic meningitis may simulate the tabetic condition in spite of a quite different course; it is then known as syphilitic pseudotabes. Likewise, the meningovascular type may be erroneously diagnosed as paresis and *vice versa.*

Charts I to IV outline the changes usually found in the spinal fluid in the different types of neurosyphilis and offer some possible aids to differentiation.

CHART I

SPINAL FLUID FORMULÆ IN MENINGOVASCULAR AND TABETIC NEUROSYPHILIS

Wassermann reaction.	Cells.	Total protein.	Globulin.	Gold-sol.
Positive in 0.05 to 1 c.c.; 40 per cent. negative with 0.2 c.c. Pure vascular neurosyphilis usually negative with 1 c.c.	Tabes. 0 to 200+. Average 25 to 50.	17 to 150 mgm. per 100 c.c. Average 78.	0 to ++++	0122100000 0134431000 3332100000 4443210000 5555431000
	Meningovascular and acute meningitis. 200 to 2000.	Average 99 mgm. per 100 c.c.		
	Chronic. 0 to 200+.	Average 73 mgm. per 100 c.c.		
	Vascular, often no increase.	Average 50 mgm. per 100 c.c.		

CHART II

VARIETIES OF SPINAL FLUID FORMULÆ IN MENINGOVASCULAR NEUROSYPHILIS

Wassermann reaction.	Cells.	Total protein.	Globulin.	Gold-sol.	Remarks.
1. Positive 0.6 c.c.	90	70	++	0244310000	Average.
2. Positive 0.4 c.c.	1200	118	++++	4443210000	Acute meningitis.
3. Positive 1 c.c.	2	45	+	0122100000	Pure vascular.
4. Positive 0.05 c.c.	40	130	+++	5555431000	Paresis sine paresi asymptomatic.
5. Positive 1 c.c.	10	30	+	1233210000	Mild.
6. Negative	35	35	+	Negative.	Mild meningitis.
7. Negative	75	50	++	4443100000	Infrequent.

CHART III

VARIATIONS OF SPINAL FLUID FORMULÆ IN TABETIC NEUROSYPHILIS

Wassermann reaction.	Cells.	Total protein.	Globulin.	Gold-sol.	Remarks.
1. Positive 0.6 c.c.	25	70	++	0244310000	Average.
2. Positive 0.05 c.c.	75	95	+++	5555421000	Not rare.
3. Positive 1 c.c.	40	30	+	Negative.	Relatively inactive.
4. Negative	50	50	++	0244310000	Infrequent.
5. Positive 0.4 c.c.	4	25	+	Negative.	Infrequent.
6. Negative	30	35	+	Negative.	Infrequent.
7. Negative	3	17	0	Negative.	Burned out or stationary.

CHART IV

SPINAL FLUID FORMULÆ IN PARETIC NEUROSYPHILIS

Wassermann reaction.	Cells.	Total protein.	Globulin.	Gold-sol.	Remarks.
Positive in 0.05 to 0.2 c.c. in 95 per cent.	0 to 200. Average	50 to 150 mgm.	+++	5432100000	Unusually weak.
Slightly weaker reaction rarely found.	25 to 50.	per 100 c.c. Average 89.		5554321000	Average.
				5555555555	Unusually strong.

Treatment.—Each case of neurosyphilis presents a different therapeutic problem. The author is firmly convinced that no definite generalization is permissible, and that the routines supposed to be applicable to many different types of cases are illogical and reprehensible. The following outline of some very fundamental principles of treatment is based entirely upon the author's personal experience, and may not agree at all with the beliefs of various authorities.

Care of the *general hygiene* of the patient is one of the important features of the treatment of all types of neurosyphilis. Many individuals improve when they have plenty of rest, fresh air, and good food, receive hydrotherapy, and have their somatic defects corrected. Co-ordination exercises are of the greatest importance in the ataxic stage of tabes, and often bring marked symptomatic improvement.

The preparations used for *specific treatment* fall into various groups, which will be discussed separately.

The *iodids* cannot be considered as curative and are only adjuvants in treatment, although in either small or extremely large doses they occasionally give symptomatic relief in meningovascular syphilis.

Mercury sometimes produces satisfactory changes in mild meningovascular neurosyphilis when administered as an ointment, or intramuscularly or intravenously. Given by mouth it is of little or no value. Mercurials are practically always ineffectual in the treatment of tabetic or paretic neurosyphilis. While they possibly may be useful when administered in conjunction with other drugs, it must be remembered that they are often distinctly harmful because they reduce the general nutrition of the patient.

Intravenous injection of *arsphenamin* is a successful form of treatment in a fair number of cases of meningovascular neurosyphilis. It is occasionally effective in tabetic neurosyphilis and in rare instances causes remissions or even arrest of the paretic type. To be used with any degree of success, this preparation should be given frequently for a long period of time (*i. e.*, twice a week for many months before rest periods are introduced). The author feels that the addition of *subarachnoid and intraventricular injections of arsphenaminized serum* (method of Swift and Ellis) to the intravenous therapy greatly increases its efficacy. When the spinal cord is involved (meningeal and tabetic neurosyphilis) intraspinal injections in the lumbar region are often effective. If the lesions are in the upper part of the cord, however, or within the cranial vault, such serum should be injected into the cisterna magnum or into the cerebral ventricles, since it is thought that substances injected into the lumbar subarachnoid space either do not reach the upper cord or brain, or else reach it in such small quantities as to be of little avail. Meningovascular neuro-

syphilis and tabetic neurosyphilis, if not unusually malignant or far advanced, are usually much benefited by this type of therapy if treatment is continued for a sufficiently long period. The optimum frequency of the subarachnoid injections depends on the severity of the condition and the reaction of the individual. The intervals may vary from about three days to a month.

A "serological cure" is to be expected in the majority of cases of meningovascular and tabetic neurosyphilis. Paretic neurosyphilis responds to treatment in only the relatively early stages, and then usually only to very intensive intravenous administration of the arsphenamins supplemented by intraventricular, intracisternal, and intraspinal injections. The Ogilvie method of re-enforcing the Swift-Ellis serum by the addition of 0.2 to 0.5 mgm. of arsphenamin is advocated by many physicians, although it causes very severe reactions. The use of mercurialized serum, as advocated by Byrnes, is also approved by many. The spinal drainage after arsphenamin injections, which is advocated by Dercum, Early, and Gilpin, is frequently used, but in the author's experience has not proved as satisfactory as the injection of serum. In this treatment, shortly after the intravenous injection of arsphenamin, all the fluid which will is allowed to run out of the lumbar needle, and 20 to 40 c.c. additional is aspirated.

Tryparsamid is a relatively new *arsenical* which is said to have greater penetrability into the nervous system than the arsphenamins. It has the great advantage of being simple to administer (about 3 grams being introduced intravenously), but its true value has not yet been determined. Up to the present time there has been great optimism about it, especially in the treatment of meningovascular and early paretic neurosyphilis. It probably is best used in conjunction with other methods of treatment. Its one disadvantage is that it tends to produce amblyopia. In the author's experience it has been a most valuable addition to other drugs.

In the treatment of general paresis especially, and of some other malignant forms of chronic neurosyphilis, the effect of inducing *malaria* or *relapsing fever* has been tried. The patient is inoculated with blood taken from individuals with one or the other of these two diseases. After malarial inoculations patients are allowed to have eight to twenty paroxysms. The induced relapsing fever is permitted to run its course. Reports of the results have been very encouraging, and indicate that there is a remission in 35 per cent. of the paretic patients treated.

Probably much improvement can be brought about in most cases of neurosyphilis, including the paretic type, by one form or another of intensive treatment. In the last few years a new optimism concerning such therapeutic possibilities has arisen.

HARRY C. SOLOMON.

DISEASES OF THE MOTOR TRACT

Amyotrophic Lateral Sclerosis. The first complete description of amyotrophic lateral sclerosis was given by Charcot in 1865. It is a disorder which begins in adult life, and is characterized by muscular atrophy associated with motor weakness, increased tendon reflexes, and spasticity dependent upon symmetrical degeneration of the anterior horn-cells of the

spinal cord and the pyramidal tracts. It terminates in atrophy of the bulbar nuclei with bulbar symptoms.

Etiology.—The cause is unknown. It is probably, however, an abiotrophy, *i. e.*, a loss of potentiality of the motor system so that the stress of advancing years cannot be withstood. The writer has seen this type of sclerosis develop after chronic lead poisoning. It bears no relation to infectious diseases or syphilis, although syphilis may evoke a very similar syndrome.

Morbid Anatomy.—The lesion is essentially a premature necrosis of the motor system. The cells of the anterior horns of the spinal cord and the pyramidal tracts degenerate, and later the cells of the motor nuclei in the pons and medulla oblongata also become atrophic. Spiller has traced the degeneration of the pyramidal tracts upward from the spinal cord to the cerebral cortex. In the beginning the lesions are most pronounced in the gray matter of the cervical segments of the cord; therefore, the muscles of the hand are affected early.

Symptoms and Course.—The disease begins in middle life, without preference as to sex; it rarely occurs as early as the thirtieth year. In typical cases symptoms of spinal muscular atrophy, of primary lateral sclerosis, and later of progressive bulbar palsy are associated. The *muscular wasting* begins insidiously; the hands first present evidence of wasting of the thenar and hypothenar muscles and interossei; the condition gradually extends to the shoulders. In this respect it resembles the Aran-Duchenne type of muscular atrophy, but differs from it in that the limbs may show moderate spasticity, increased tendon reflexes, and Babinski signs. Not infrequently the limbs of one side are affected more severely than those of the other. A unilateral type of this disease has been described. Within a period of six to eight months all four limbs may become decidedly paretic. During this stage the arms are partially flexed at the elbow, and the hands are pronated, greatly wasted, and present the Simian appearance. The tendon reflexes are always preserved or exaggerated. Fibrillary tremors and muscular atrophy are conspicuous features. Electrical examination generally reveals complete or partial *reaction of degeneration*. *Motor weakness* may be marked and, because the pyramidal tracts are involved, is much greater than that resulting from muscular atrophy alone. After the condition has existed for one or two years, or a much shorter time in some cases, the patient becomes bedridden. *Pain* is absent. *Sensation* is preserved. There are no *bladder and rectal disturbances*. *Atrophy*, *rigidity*, and *paresis* are the sole symptoms. Later, however, *bulbar symptoms* appear; these, as a rule, do not attain full development until the last stages of the disease. Sometimes, however, they appear simultaneously with the onset of weakness of the limbs. *Dysarthria*, and later *anarthria* and *dysphagia* become marked. Food is swallowed with difficulty, and fluids are regurgitated through the nose. *Mastication* is interfered with, and the movements of the lips, tongue, palate, and jaw are paretic. In addition to the other symptoms the patient presents the syndrome of progressive glosso-pharyngo-labial paralysis.

Prognosis.—The prognosis is always unfavorable. Most cases terminate fatally before the third year.

Treatment.—No adequate method of treatment is known. Strychnin seems to be somewhat beneficial.

Primary Lateral Sclerosis (*Spastic Spinal Sclerosis of Erb*).—Definition.—Primary lateral sclerosis was first described by Erb in 1875 as a condition characterized by gradually increasing motor weakness, spasticity, and exaggeration of tendon reflexes which ran a chronic course for many years. He attributed this syndrome solely to primary degeneration of the motor tracts.

Etiology.—The cause is unknown. The disease probably depends on an inherent lack of resistance of the motor system due to defective development—a condition called by Gowers "abiotrophy." Hereditary and familial tendencies have been observed by Strümpell, but the disease occurs sporadically.

Morbid Anatomy.—In pure primary lateral sclerosis the pyramidal tracts alone degenerate. This lesion may not be strictly symmetrical. No other alterations or evidences of inflammation are present. Since the distal or the lower portions of the pyramidal tracts degenerate first, the symptoms are those of crural paraplegia.

Symptoms and Course.—The disease begins insidiously in adult life and tends to progress very slowly; it may become arrested in its course. The symptoms are those of *spastic paraplegia, i. e.*, weakness of the lower limbs, increased tendon reflexes, spasticity, ankle clonus, patellar clonus, and the Babinski sign. The ability to walk is maintained until late, but owing to weakness and spasticity locomotion becomes slow and difficult. Rigidity of the adductor muscles of the thighs produces the so-called "*scissors gait.*" The spasticity of the muscles is generally greater than the motor weakness. The course is slow; the symptoms may persist for twenty-five years or even longer. All forms of *sensation* are preserved. *Pain* does not occur. As a rule the disease is bilateral, but one limb may be affected more than the other. Rarely the upper limbs are similarly affected. A unilateral type of the disease has been observed by Mills.

Diagnosis.—The disease is uncommon, and because the symptoms may closely simulate degeneration of the pyramidal tracts from other causes, a *clinical diagnosis cannot be made.* Nevertheless, the disease may be suspected whenever additional symptoms are lacking, especially alterations in sensation; and also when all other conditions associated with spastic paraplegia as a symptom can be eliminated—multiple sclerosis, combined sclerosis, syphilis, caries of the vertebræ, amyotrophic lateral sclerosis, hematomyelia, trauma, and, most particularly, spinal tumor and the hereditary form of spastic spinal paralysis.

Treatment.—Division of the posterior roots or cutting of the peripheral nerves (Stoeffel's method) may, by diminishing the degree of spasticity, be of benefit. No method of treatment has succeeded in averting the disease.

Progressive Bulbar Palsy (*Progressive Glosso-pharyngo-labial Paralysis*). Definition.—Progressive bulbar palsy is a rare disease of advanced life, characterized clinically by difficulty in speech, deglutition, mastication, and phonation, due to atrophy of the muscles of the lips, tongue, palate, pharynx, and larynx, and dependent upon degeneration of the cells of the motor cranial nerves situated in the pons and medulla oblongata.

Etiology.—The cause is unknown. It is doubtful whether heredity and congenital tendencies play a part. Congenital inferiority of the nervous structures involved may, however, cause premature loss of function.

Like the other conditions mentioned in this chapter, this disease is usually classed among the abiotrophies. Syphilis does not play an etiological part, not do infectious diseases, but a similar syndrome has been known to follow diphtheria and mumps.

Morbid Anatomy.—The cells forming the motor nuclei of the cranial nerves undergo degeneration, especially those of the hypoglossal, facial, and motor glossopharyngeal and spinal accessory nerves; sometimes the nucleus of the motor portion of the trigeminal nerve is also affected. The cells eventually become completely atrophied, and consequently the muscles innervated by them atrophy. The third nerve, as well as the sensory nuclei, usually escapes. In typical cases no other changes occur.

Symptoms and Course.—The disease begins in adult life, usually, however, not before the fiftieth year. An infantile form has been recorded which differs from the adult type in certain details, especially by its hereditary and familial tendencies. The first manifestations are generally increasing difficulty in articulation, especially for lingual and labial sounds. Puckering the lips, as in whistling, becomes impossible. Because of paralysis of the soft palate the voice assumes a nasal character. The larynx becomes affected, and the intense defect renders speech unintelligible. Atrophy of the lingual muscles causes inability to protrude the tongue, which shows fibrillary tremors. Because of weakness of the tongue there is also difficulty in mastication; this may be increased if the muscles of mastication are simultaneously involved. Paralysis of the pharynx may be slight at first, but tends to progress, making deglutition impossible. When this occurs, there is great danger that food may pass into the larynx and produce bronchitis or aspiration pneumonia. The muscles supplied by the oculomotor nerves are not involved. The tendon reflexes of the limbs are preserved, and are apt to be exaggerated. The disease is purely motor in all its manifestations. Sensation is never disturbed, and intelligence is preserved. The symptoms generally develop gradually, reaching their height within three years. The condition terminates fatally because of inanition.

Diagnosis.—It may be difficult to differentiate this form of paralysis from *pseudobulbar palsy*, a condition caused by multiple lesions in the cerebrum in which muscular atrophy, fibrillary tremors, and the reaction of degeneration do not occur, whereas symptoms of pyramidal tract involvement are generally present. *Myasthenia gravis* can generally be recognized by its essential characteristics, *i. e.*, increase in the intensity of the symptoms by fatigue, and improvement in them after rest; the absence of atrophy; the myasthenic electrical reaction; and the implication of the ocular muscles. Other forms of bulbar palsy caused by tumor, vascular disease, or encephalitis affecting the pons and medulla oblongata can be distinguished by the frequency of associated sensory disturbances, and especially the more rapid mode of onset and the presence of symptoms of pyramidal tract involvement.

Treatment.—No successful method of treatment is known. Especial attention must be directed to maintaining nutrition and to the avoidance of respiratory complications induced by choking and the inspiration of food particles.

Progressive Spinal Muscular Atrophy.—Definition.—Progressive spinal muscular atrophy, also known as the Aran-Duchenne type of muscu-

lar atrophy and as chronic anterior poliomyelitis, is characterized by progressive muscular wasting dependent upon degeneration of the cells of the anterior horns of the spinal cord. It usually begins in the small muscles of the hands, but may attack the muscles of the shoulders first. At onset it may be unilateral, but it soon becomes bilateral.

Etiology.—The exact cause is unknown. Whether infections or intoxications bear any relation to it is extremely uncertain. Although syphilis may produce muscular atrophy, it is not a usual cause of progressive spinal atrophy. Exceptionally the disease has been known to develop after an arrested attack of acute anterior poliomyelitis, an infectious disease that may leave the anterior horn-cells weak. Acute anterior poliomyelitis, however, is not in itself a cause of progressive spinal atrophy. Heredity plays no part. Since the symptoms appear in middle life, age seems to be the most important factor. The condition is regarded as belonging to the group of disorders called by Gowers "abiotrophies," a term coined to designate the disturbance in which, because of a supposed defect in development, the cells of the spinal cord are incapable of resisting the stress of advancing years, and consequently undergo early degeneration.

Morbid Anatomy.—The characteristic lesions are atrophy and degeneration of the large nerve-cells of the anterior horns of the spinal cord. The anterior motor roots may undergo proportional atrophy. Hemorrhages have been observed within the gray substance of the cord. In typical cases the white substance of the cord is not involved, but necropsies have, nevertheless, revealed involvement of the pyramidal tracts which had produced no symptoms. If the pyramidal tracts are involved sufficiently to produce symptoms, the diagnosis of progressive spinal muscular atrophy is not justified, for the condition should then be classed as amyotrophic lateral sclerosis, a more common morbid process.

Symptoms and Clinical Course.—Except in the infantile type, the symptoms of progressive spinal muscular atrophy rarely begin before the thirtieth year of life. *Muscular wasting* begins insidiously and progresses slowly. The rate of progress and distribution of the atrophy may vary considerably in different cases. It generally first affects the small muscles of the hands, the interossei, and the muscles of the thenar and hypothenar groups; but in some cases (those of the scapulohumeral type) described first by Vulpian, the condition begins in the muscles of the shoulder and upper arm. Rarely it begins in the lower limbs, especially in the peroneal muscles. Muscular hypertrophy never occurs, the disease differing in this respect from progressive muscular dystrophy. Awkwardness of the hands because of weakness may first attract attention to the condition. The degree of weakness varies directly with the extent of the muscular atrophy. Spinal atrophy was formerly distinguished from chronic poliomyelitis[1] on the basis that in the latter condition weakness preceded muscular atrophy, whereas in spinal atrophy wasting preceded motor weakness. This view, however, is no longer tenable. Extension proceeds very slowly; at first only a portion of one muscle and then another is implicated. Fibrillary tremors of the affected muscles are very common, but are not essential in confirming the diagnosis, since they occur also in other affections. The atrophy

[1] The term "chronic poliomyelitis" is undesirable, for it leads to confusion. It is synonymous, however, with "spinal muscular atrophy." Acute anterior poliomyelitis is an altogether different disease.

extends most frequently from the hands to the extensors and flexors of the forearm, and several years usually elapse before the muscles of the upper arm, shoulder, and girdle are affected. In the scapulohumeral type, however, the reverse order of extension occurs. The muscles of the upper arm, shoulder, and back (the infraspinatus, trapezius, serratus magnus, etc.) are affected first; the muscles of the forearm and hands are involved later. Generally several years elapse before the upper limbs and shoulders suffer severe change. The lower extremities are not, as a rule, wasted until late. The sphincter muscles are never involved. When well established the disease is always bilateral, but not infrequently in the early stage it may be unilateral for weeks or even months. The atrophy is not always exactly symmetrical, but there is a decided tendency for it to become so. The early involvement of the hands is explained on the theory that the muscles most used are probably affected early. The tendon reflexes are absent or greatly diminished. Exaggeration of the tendon reflexes is a symptom of disease of the pyramidal tract, and when associated with muscular wasting renders the diagnosis of spinal muscular atrophy extremely doubtful. Such conditions should be considered amyotrophic lateral sclerosis, an allied condition that runs a much more rapid course and ends with bulbar paralysis.[1] Objective disturbances of sensation and acute pain never occur, but a dull ache, the result of overuse of the weakened muscles, develops. The reaction of degeneration may be present, but frequently there is only a diminution of the electric response in the muscles in proportion to the degree of atrophy.

Prognosis.—The disease is essentially progressive. Very exceptionally, it is believed, remissions occur. There is doubt whether the condition may be arrested. The muscular wasting continues gradually for a period of fifteen years or more. The patient usually dies of an intercurrent affection.

Treatment.—No method of treatment capable of checking the progress of the disease is known. Overfatigue of weakened muscles should be avoided. Electricity, massage, rest, and tonics, especially strychnin, may be of value.

Progressive Spinal Muscular Atrophy of Childhood of Familial or Hereditary Character (*Werdnig-Hoffmann Type*).—Definition.—Progressive spinal muscular atrophy of childhood is a condition first described by Werdnig and later by Hoffmann, which differs from the adult form of spinal atrophy in its hereditary and familial tendencies. It develops in the early years of life, involving first the muscles of the pelvic girdle, and extending toward the ends of the limbs. It is dependent on degeneration of the anterior horn-cells and the peripheral motor nerve-fibers, and on alterations of the crossed pyramidal tracts.

Etiology.—The cause is unknown. Several children of the same parents may be affected, but isolated cases also occur. Its relationship to *myatonia congenita* is very doubtful. The condition is most probably dependent upon a defect in the development of the nervous system (abiotrophy).

Morbid Anatomy.—In Hoffmann's patients there was degeneration of

[1] Many authorities believe that "amyotrophic lateral sclerosis" and "progressive muscular atrophy" are two clinical manifestations of one disease, the morbid process of which is a combined degeneration of the anterior horns and of the motor tracts. If degeneration of the anterior horns *precedes* that of the motor tracts the syndrome produced is necessarily that of progressive muscular atrophy.

the multipolar cells of the anterior horns of the spinal cord, intense degeneration of the anterior roots, and less marked change in the peripheral nerves, together with degeneration of the crossed and direct pyramidal tracts. The muscles undergo simple atrophy.

Symptoms and Course.—The disease begins in childhood and progresses slowly. The child either never learns to walk or loses the ability to do so. The condition is manifested by weakness and atrophy of the muscles of the trunk and pelvic girdle, the iliopsoas, quadriceps femoris, and later of those of the upper limbs and neck. The proximal portions of the limbs are affected first, the change then slowly extending to the hands and legs. A year or more elapses before the distal portions of the limbs are affected. The wasting of muscles is generally symmetrical, and so uniform is the atrophy that in the beginning it may be concealed by fatty tissue. The tendon reflexes are abolished. Fibrillary tremors may be present, but frequently are absent. Hypertrophy never occurs. Sensation is not disturbed. Bulbar symptoms sometimes develop, but are rare. The disease is progressive, and generally ends fatally before the seventh year.

Diagnosis.—Because of the familial tendencies and the implication of the proximal portions of the limbs, the greatest difficulty may be experienced in differentiating this condition from *progressive muscular dystrophy*, but the absence of hypertrophy and pseudohypertrophy and the presence of fibrillary tremors of the muscles serve to distinguish it. *Congenital myatonia* differs from it in being congenital in origin and without familial tendencies, and by the proportionately greater involvement of the muscles of the trunk at a much earlier age. It should not be confused with a form of *primary* or *idiopathic wasting* that occurs in very young babies because of failure of nutrition.

Prognosis.—As in the adult form, the disease generally ends fatally as the result of intercurrent disease. Recovery is unknown.

The Neurotic Form of Progressive Muscular Atrophy (*Charcot-Marie-Tooth Type, Peroneal Atrophy*).—The neurotic type of progressive muscular atrophy was described independently in 1886 by Charcot and Marie in France, and by Tooth in England.

Etiology.—The exact cause is unknown. Since familial and hereditary tendencies are marked, parents and their children frequently being affected, the condition is regarded as being dependent on developmental defects of the nervous system; but sporadic cases also occur.

Morbid Anatomy.—The lesions consist of degeneration of the posterior columns of the spinal cord, atrophy of the cells of the anterior horns, and alterations of the cells of Clarke's columns, with less marked changes of the peripheral motor nerves. It is not known which of these structures are affected first.

Symptoms and Course.—The disease usually begins in early adult life, most frequently before the twenty-second year. It may be transmitted directly through parents to their children, or may skip a generation. Males are believed to be affected more often than females. The onset is insidious and the course slowly progressive. Prolonged remissions occur. In typical cases there is first noticed a slight difficulty in walking, due to weakness of the muscles supplied by the peroneal nerves (the peronei, extensor communis digitorum, and the small muscles of the foot). Consequently *pes varus* and

equinovarus may develop early. Ankylosis of the ankle-joints may occur. Gradually all the muscles below the knee become atrophic, in contrast to those of the thigh, which appear normal. After one or more years the muscles of the hands are affected, the wasting gradually extending to the more proximal portions of all the limbs. The shoulder, trunk, and facial muscles usually escape. A characteristic feature of the disease is the early implication of the distal portion of the lower limbs, with integrity of the proximal portion. Subsequently, however, the distal portions of the upper limbs are involved, with relatively slight wasting of the proximal muscles. This may progress for years. The tendon reflexes usually disappear. Unlike other types of muscular atrophy this disturbance slightly affects sensation in the distal parts of the lower limbs. Paresthesia, numbness and tingling, and even pain may at times be present. Electric tests may reveal the reaction of degeneration in the affected muscles.

Prognosis.—After the disease has fully developed the patient may live for many years. Improvement is rare. Death is generally due to an intercurrent affection.

Treatment.—No method of treatment has proved successful.

Williams B. Cadwalader.

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HEREDITARY AND FAMILIAL DISEASES OF THE NERVOUS SYSTEM

The nervous system, like the other structures of the human body, is not always complete or normal at birth. Furthermore, it may appear to be normal at birth, and for a number of years thereafter; then, suddenly or gradually, there develops some defect in function or structure which manifests itself as a syndrome or disease. The more important of these disturbances, including those which occur in more than one member of a family, are briefly described here.

Malformations of the Brain and Meninges.—At birth the brain may be entirely absent—*anencephalia*—or absent except for the cerebellum and part of the basal ganglia. Such conditions are associated with *acrania*. Sometimes when development is arrested the cerebrum remains single instead of separating into two hemispheres, there is only one ventricle, and the rudiments of the eyes unite to form one eye (*cyclopia*). When the skull is abnormally small (*microcephaly*) and the brain is also very small and

defectively developed the condition is known as *micrencephaly*. Greater development of one side of the brain than of the other is called *asymmetry*. In *porencephalus* a cyst is connected with the ventricle and there is lack of cerebral substance. In *nuclear aplasia* certain cranial-nerve nuclei are absent or imperfectly developed. When the oculomotor nuclei are aplastic, ptosis of the upper eyelids and weakness or absence of movement in the eyeball ensue. This condition may be present at birth or develop slowly and progressively in adult life, producing bilateral ptosis, paresis of the extra-ocular muscles, and, later, paresis of the internal muscles of the eye. It is not always associated with other involvement of the central nervous system, and when it occurs alone is probably due to a congenital imperfection of the nerve-cells of the oculomotor nuclei which was not apparent at birth.

Hydrocephaly, which is at times present at birth, is characterized by abnormal enlargement of the head and dilatation of the ventricles of the brain at the expense of the brain substance which, as a rule, is flattened into thin sheets surrounding the ventricles. It is usually internal and bilateral, but occasionally the ventricular distention is restricted to one lateral ventricle as the result of either a developmental anomaly of the brain or of some lesion in the ventricular walls. *External hydrocephaly* is a comparatively rare condition characterized by accumulation of fluid in the distended subarachnoid space over the surface of the brain, and by atrophy or shrinking of the brain substance. Moderate hydrocephalus is not incompatible with normal intelligence, and may even be associated with brilliance. Generally, however, it is associated with some degree of mental impairment, and often also with weakness of the limbs, because the pyramidal tracts are degenerated or ill developed. The congenital form is frequently caused by total or partial obstruction of the aqueduct of Sylvius; this prevents circulation of the cerebrospinal fluid from its point of formation in the choroid plexuses of the lateral and third ventricles to the fourth ventricle, and thence to the subarachnoid space through the foramina of Magendie and Luschka. When normal absorption of the fluid in the subarachnoid space is thus prevented, its accumulation in the lateral and third ventricles produces *internal hydrocephalus* (*obstructive internal hydrocephalus*). The *diagnostic test* for this is injection of a neutral dye (indigocarmin), which is specially prepared, into one of the lateral ventricles; and, a few minutes later, removal of some of the spinal fluid by lumbar puncture. If the dye does not appear in the fluid thus obtained, there is obstruction in the Sylvian aqueduct or in the foramen of Monro. By introducing air into the lateral ventricle (Dandy's ventriculography) the exact site of the obstruction can often be determined. The *prognosis* of congenital hydrocephalus is serious, although in many children the disease is arrested, and physical and mental development is more or less normal. Measurement of the skull at regular intervals enables the physician to determine how rapidly the condition progresses. *Treatment* has not proved very successful. Removal of fluid from the ventricles is easy before the fontanels have closed, but is of little, if any, benefit; it is not without danger of sudden collapse if performed too rapidly. Dandy and others have actually put sounds and, later, tubes through partially obstructed Sylvian aqueducts, with good results in a few cases. This is, of course, a difficult and dangerous operation.

Meningocele is hernia of the membranes of the brain through a cleft in the skull; *encephalocele* is also protrusion of the brain substance, usually in the occipital region in the median line.

Spina bifida is a congenital defect of the sacral or lower lumbar vertebræ, which is very often associated with protrusion of the meninges. These form a lump under the skin which is soft, and contains cerebrospinal fluid, and, at times, portions of the cauda equina or of the spinal cord itself. Spina bifida is apt to be associated with other developmental anomalies, such as cervical rib, syringomyelia, or hydrocephaly. Sometimes when the bony defect is slight there is no lump (meningocele), but a tuft of hair or a pad of fat lies over the lesion; this condition is called *spina bifida occulta*. Both *spina bifida* and *spina bifida occulta* may produce a definite syndrome. The lower limbs are weak, and often much atrophied below the knee. There is incontinence of urine or, perhaps, enuresis. Trophic ulcers are very prone to develop on the soles of the feet, either spontaneously or as a result of slight injury to the skin (a blister, for example, produced by a badly-fitted shoe). The ankle-jerks are absent, as a rule. This condition may manifest itself only at puberty when the more rapid growth of the spine, compared with the spinal cord and roots within, causes pernicious traction on the cauda equina, which results in functional disturbance of the sacral and lower lumbar motor and sensory roots. The *prognosis* depends on the extent of the hernia and on what it contains. The sac, if large, may rupture and cause death at once, or later from purulent meningitis. Surgical intervention has saved some patients. If the sac contains only fluid and meninges, the chance of cure is greater than when it also contains nerve structures. The mortality of the operation is very high in the first months of life, and operation should consequently be deferred as long as possible. Recovery is far better in patients over two years of age than in younger subjects.

Defects of the Spinal Cord.—Entire absence of the spinal cord (*amyelia*) is associated with anencephaly. *Amyelencephaly* is absence of both brain and spinal cord. *Atelomyelia* is lack of development of the cord, *e. g.*, absence of the pyramidal tracts. *Asymmetry* of the cord occurs with possibly defective development of one pyramidal tract. In *heterotopia* the gray portions of the cord are displaced so that patches of gray matter are scattered among the bundles of white fibers: this condition is sometimes produced artificially at autopsy by rough removal of the cord. *Micromegaly*, the presence of an abnormally small spinal cord, is associated with such conditions as Friedreich's disease. A spinal cord is seldom completely double (*diplomyelia*), and may be so in only a few segments. The condition is due to failure of the central canal of the cord to close or contract normally. This duplication of the canal is not as rare as some of the other anomalies.

Types of Mental Deficiency.—Mental deficiency is of many degrees and grades. In some patients there are obvious organic defects of the brain (microcephaly or hydrocephaly, for example), while in others the brain appears to be normal even on microscopical examination.

The Profound Idiot.—This is the lowest type of mental defective. He is usually of small size, physically abnormal, and, at any age, more helpless than the normal infant. He has apparently no mentality.

The Superficial Idiot.—Slightly higher in the scale, but still in the

idiot class, is the superficial idiot. Such individuals may be able to speak very imperfectly, can walk, and perform other muscular movements with better co-ordination than can the profound idiot. They are often mischievous, ill-tempered, and difficult to manage.

The Idio-imbecile and the Imbecile.—The third grade is the idio-imbecile, and the fourth, the imbecile, which includes three grades—low, middle, and high. Imbeciles can be trained in the various arts and trades, but require a long apprenticeship and a good deal of supervision, preferably in a colony.

The Moral Imbecile.—This type is not only mentally but morally deficient, and needs constant supervision. He can, like other imbeciles, be trained, but must be carefully watched because of his tendency to do evil things.

Backward Children.—The very large class of backward children can be trained to fill a place in the outside world, since their mental processes are normal, but slower than the average. Some of these individuals appear perfectly normal except during excitement, illness, or under other adverse conditions.

Amaurotic Family Idiocy.—A type of idiocy with peculiar pathology is the so-called amaurotic family idiocy (Tay-Sachs disease) which occurs almost exclusively in Jewish children and is fatal within two years or a little more. It is associated with optic atrophy and blindness, and the appearance of a cherry-red spot at the macula in each retina. The nerve-cells throughout the brain and spinal cord undergo characteristic degeneration, becoming greatly enlarged (ballooned); and the Nissl substance becomes fragmented and collects about the eccentric nucleus. The neurofibrils are pushed to the periphery of the cell body. This form of idiocy may affect several children in one family.

Mental Deficiency and Epilepsy.—At times mental deficiency and epilepsy are associated. Epilepsy occurs in some cases in more than one member of a family.

LITTLE'S DISEASE

(*Congenital Spastic Stiffness of the Limbs*)

The one well-known disease of the pyramidal tracts which is associated with little or no mental defect is Little's disease. This is congenital or infantile in origin and results from lack of development (*agenesis*) of the pyramidal tracts which leads to atrophy or sclerosis of the lateral columns of the spinal cord. The condition is sometimes seen in twins. The symptom-complex can, no doubt, be produced by a number of conditions which operate before or at the time of birth, but its most important cause is premature birth. Meningeal hemorrhage and congenital syphilis are responsible for some cases, and trauma to the head during difficult labor, even without visible hemorrhage of the brain, may arrest development of the pyramidal tracts. The symptoms can be observed usually within a year of birth, but may at times not appear for a number of years. Patients begin to walk very late, and manifest the well-known "cross-legged" progression due to spastic adduction of the thighs. The arms are less involved. The deep reflexes are exaggerated, especially at the knee and ankle, and there is often a double Babinski sign. When the condition is mild it responds slowly to massage and any necessary orthopedic therapy,

such as tenotomy. Some of the posterior roots of the spinal nerves supplying the spastic muscles have been resected, at times with favorable results. If the condition is severe the patient gradually becomes more and more helpless as the size and weight increase. Death often results from intercurrent disease before he reaches twenty years of age.

Spastic Cerebral Diplegia.—Distinct from Little's disease is spastic cerebral diplegia (birth palsy), the lesion of which is characteristically more extensive and is usually a hemorrhage of the brain at the time of birth. In addition to the diplegia there is epilepsy and defective speech and mentality.

Hereditary Hemiplegia.—This is a rare form of hereditary hemiplegia which is sometimes associated with atrophy of the paralyzed side.

Hereditary spastic spinal paralysis is a rare disease which affects several members in many generations of one family. It causes slowly progressive paralysis of the legs, which begins at about the age of five and continues twenty or thirty years.

HEREDITARY SPINAL ATAXIA

(*Friedreich's Disease*)

A common disease which begins between the age of six and fifteen years, and may affect several brothers and sisters, is hereditary spinal ataxia. The lesion involves the posterior columns and pyramidal tracts of the spinal cord, and there is some degeneration in the direct cerebellar tracts and cerebellum. These changes lead to ataxia, weakness in the legs, pes cavus, scoliosis, sometimes manus cava, and occasionally to nystagmus and tremor of the head. Two or more children of one family may have the scoliosis and characteristic deformity of the feet, while one or more may manifest the complete syndrome, which includes not only evidences of tract degeneration in the spinal cord but also well-marked signs of cerebellar disturbance such as nystagmus, nodding of the head, syllabic speech, and asynergy of both arms and legs. The bilateral deformity of the foot is striking, the dorsum is high, the arch deeply hollowed, and the great toe hyperextended at the metatarsophalangeal joint and flexed at the phalangeal joint. There is a kind of "permanent Babinski sign." The ankle-jerks are absent and also the knee-jerks. The deep reflexes in the arms may be lost in the late stages of the disease. Occasionally, in well-marked cases, the palms of the hands are hollowed, just like the soles of the feet, and the fingers are hypotonic and become hyperextended when the arms are held straight out in front with the palms down. The bladder and rectal sphincters are not involved and there is no pain or loss of sensation. At times, when the cerebellar signs are more marked than those referable to the spinal cord, the condition may resemble Marie's hereditary cerebellar ataxia.

Hereditary cerebellar ataxia, which is allied to Friedreich's disease, develops somewhat later in life and causes more degeneration in the cerebellum than in the spinal cord. Many of these hereditary defects in the structure of the nervous system (*abiotrophies*) are not true to type, but merge one into the other, as these two diseases quite commonly do.

FAMILY PERIODIC PARALYSIS

This is a rare hereditary disease which begins in early life and lasts for many years. The paralysis comes on very often during the night and is a flaccid palsy of legs, trunk, and arms, without sensory disturbance or in-

volvement of the cranial nerves. It lasts for between a few hours and a few days, and is associated at times with some dilatation of the heart.

HEREDITARY CHOREA

(Huntington's Chorea)

This disease begins in middle life and affects several generations as well as more than one member of a single generation. It is progressive and degenerative in type, and is associated with gradual progressive dementia. The disease is easily recognized by the jerky, irregular movements of the entire body. The gait is very much disturbed. The head is twisted about from side to side, and the shoulders are raised on one side and then on the other, with irregular, jerky, twisting movements of the hands and arms as the patient walks rather hurriedly across the room. All movements seem to be exaggerated or overdone and there is much grimacing. The patient can, by an effort of the will, control these movements for a minute or two, but they soon begin again, and, like many other involuntary movements, increase when the patient knows he is under observation. Men and women are about equally affected. Heredity is the chief etiological factor and rheumatism and other infections play no part as they do in the chorea of Sydenham. The lesion is a degenerative change in certain brain cells. The small motor cells of the caudate nucleus and the putamen are particularly affected by atrophy. Some of the pyramidal cells in the psychomotor areas are also involved—a fact which no doubt accounts for the gradual development of dementia. The choreic movements probably result from atrophy of the cells in the corpus striatum. Sometimes there is a good deal of proliferation of the glia in the brain, and, at times, there are vascular changes suggestive of encephalitis. Although the condition becomes gradually worse, some improvement may occasionally be brought about by administration of such sedatives as bromids, luminal or hyoscin, and a course of tonic treatment.

There is a type of hereditary chorea without dementia which begins earlier in life than Huntington's type—often at the age of puberty. It affects the muscles of the face and arms, but leaves the legs unaffected. Patients with this disease may lead a fairly normal, active life.

WILSON'S DISEASE

(Progressive Lenticular Degeneration)

This is a familial, somewhat rare condition. It affects young people and is associated with a peculiar "hob-nail" cirrhosis of the liver. The clinical manifestations are bilateral athetoid movements of the hands, arms, legs, and face. The face usually bears a grin which spasmodically breaks into a laugh, since there is considerable emotional disturbance. The athetoid twistings are rhythmical and increase on voluntary movement. The limbs are more or less spastic and contractures eventually develop. The deep reflexes are active, but there is no Babinski sign because the pyramidal tracts are not affected. There is no actual weakness of the muscles or loss of sensation. The abdominal reflexes are preserved. The speech is dysarthric and there is difficulty in swallowing. The disease is progressive and fatal within a few years. Postmortem examination of the brain reveals extensive changes in the lenticular nuclei, sometimes cavity formation.

APLASIA AXIALIS EXTRACORTICALIS CONGENITA

(*Pelizaeus-Merzbacher*)

This is a rare congenital and familial disease which begins in infancy, makes rapid progress at first, and later follows a more chronic course. It somewhat resembles multiple sclerosis. The chief clinical features of the disease are slowness of speech, fixation of facial expression, nystagmus, ataxia with spasticity of the legs, and mental deficiency. The lesion is an atrophy of the white matter of the brain.

HEREDITARY PROGRESSIVE SPINAL AND NEURITIC MUSCULAR ATROPHIES

There are three types of hereditary progressive spinal and neuritic muscular atrophy: the infantile form of Werdnig-Hoffman, which begins in the first or second year of life and causes weakness and atrophy of the muscles of the buttocks, back, and legs, and later of the muscles of the shoulders and neck, with final involvement of other muscles; the adult form (Dana), which is rapidly fatal, and begins at about the age of thirty or fifty years; the Charcot-Marie-Tooth form, in which the muscles of the legs (peronei muscles) and, later, of the forearms atrophy.

HEREDITARY PROGRESSIVE DYSTROPHIES

In the group of hereditary progressive dystrophies of the muscles and the nerves supplying them are included a number of conditions:

Pseudohypertrophic muscular dystrophy is, perhaps, the best known. It may affect several children in a family without any history of ancestral nervous or muscular disease. It occurs in boys much more often than in girls. At times the disease is inherited through several generations. It usually begins in childhood. The patient develops a waddling gait, falls easily, and finds difficulty in climbing stairs. He cannot rise from the ground without the use of his arms and cannot stand erect until he has "climbed up his legs" with his hands. Hypertrophy of the calf muscles becomes marked, and the muscle is hard and unnatural to the touch. The infraspinatus, supraspinatus, and deltoid, as well as certain other muscles, may also undergo hypertrophy. Lordosis develops. The child gradually becomes more helpless and the pseudohypertrophy may give place to atrophy of the muscles.

Juvenile Form of Progressive Muscular Dystrophy (Erb's Type).—In juvenile progressive muscular dystrophy the muscles of the shoulder-girdle are first affected. There is hypertrophy of some of the muscles of the shoulder-girdle, and also at times of some of those of the pelvic girdle. The thighs, deep muscles of the back, and of the upper arm become atrophic. Later atrophy takes place in the hypertrophied muscles. The face, forearm, hand, and leg muscles remain normal for a long time. The disease begins in childhood or a little later. It is one of the rarest forms of dystrophy and, like other primary myopathies, gives evidence of no change in the central nervous system.

Landouzy-Déjerine Dystrophy.—In the Landouzy-Déjerine type of dystrophy there is no muscular hypertrophy, but marked atrophy of the muscles of the face, shoulder-girdle, and arm. Those of the forearm, hand and legs, and the deep muscles of the back, as a rule, remain normal. The facial atrophy usually begins early in life, and produces a peculiar ex-

pression called the *"myopathic facies."* The lips appear thickened, and the lower lip curves downward (*"bouche de tapir"*) because of the atrophy in the orbicular muscle of the mouth. The ocular muscles and those of deglutition are not affected. The patient later develops a marked lordosis and gives the impression of a pouter pigeon because of the peculiar posture and awkward gait.

Sometimes forms of muscular dystrophy seem not to remain true to types, and in certain cases characteristic signs of at least two of these types have been seen.

MYOTONIA CONGENITA

(Thomsen's Disease)

This is a disease which usually affects several members of the same family and is transmitted from generation to generation. The muscles are so affected that at the beginning of a muscular movement it is extremely difficult to overcome a certain muscular stiffness (hypertonus). After several contractures the muscle "limbers up," but this disappears as soon as the muscle is at rest again. The disease begins very early in life and is chronic. Therapy is not usually effective, although some good temporary results have followed the use of strychnin or thyroid substance and atropin. A patient with myotonia may exhibit to a marked degree the symptoms of vagotonia.

MYATONIA CONGENITA

(Oppenheim's Disease, Amyotonia Congenita)

This is a rare disease of infants which was described by Oppenheim in 1900. Clinically it is the very opposite condition from myotonia congenita. The two terms are often confused. During the first few months of its life the child seems paralyzed—the muscles are flabby and atonic, and the deep reflexes are absent or very sluggish. The legs are most severely affected, but the trunk and arms are also involved. The arms and legs hang loosely and the child cannot move them to any great extent. The muscles do not atrophy or, at least, do not appear to. The disease is congenital and does not usually occur in more than one member of a family. Thirty per cent. of patients die within the first year. The pathology of the condition is not fully understood. Some believe the disease to be a fetal form of poliomyelitis; indeed, in one case which was under the author's observation and later came to autopsy, the lesion in the spinal cord did resemble that of anterior poliomyelitis to some extent. Oppenheim states that some patients have improved; and he considers the condition to be one of delayed development of the muscles.

MYOTONIA ATROPHICA

This is a rare disease which begins between the ages of twenty and thirty years, and is characterized by peculiar myotonic stiffness of the muscles, as well as by atrophy of special muscle groups, *i. e.*, the orbicular muscles of the eyes and mouth ("tapir mouth" and myasthenic facies), the sternomastoids, extensors of the arms, supinator longus, and the vasti muscles of the thigh. Other features are increased lacrimation and salivation, a peculiar defect in articulation, and general emaciation. The condition is most peculiarly associated with cataract of the eye; several members of one family as well as the patient with atrophic myotonia may suffer from cataract.

DYSTONIA MUSCULORUM

(*Tortipelvis, Dystonia Musculorum Deformans*)

This disease occurs commonly in Jewish children, often in several members of one family. It is characterized by peculiar, slow, tonic spasms of the muscles of the trunk and pelvis. The legs also are usually so involved that the gait is hampered not only by the rhythmical twisting of the body but also by a characteristic inversion of the feet. Consequently the patient walks not on the sole of the foot, but on its inverted lateral surface. Sometimes walking entails the greatest difficulty and absurd grotesque twisting of the body.

TERATOMAS, TERATOID AND DERMOID TUMORS, GLIOMA RETINÆ

Certain tumors of the brain and of the spinal cord which are present at birth may become manifest almost at once or, at times, not until much later in life. *Hypophyseal dermoids* are found at the base of the skull, in the sella turcica, near the olfactory lobes, or at the optic chiasm. Other intracranial dermoids are found between the medulla and pons and elsewhere. Sometimes they grow from the dura mater, often in the median line in the tentorium cerebelli. *Cholesteatoma* may occur in the bones of the skull or within the brain substance or ventricles. *Glioma of the retina* is congenital, and is reported to occur in several children of a single family.

CONGENITAL SYPHILIS

Congenital syphilis of the nervous system is not uncommon. It gives rise to syphilitic meningitis and to juvenile paresis or taboparesis. A child with congenital lues may, very soon after birth, have basilar luetic meningitis with secondary hydrocephalus and yellow spinal fluid (xanthochromia); or may develop normally until the age of five or ten years and then show symptoms of general paresis. The mentality drops, the memory becomes poor, and dementia sets in. Epileptic fits may occur as in older paretics. The deep reflexes at the ankle and knee are often absent (taboparesis) and the pupils are sometimes sluggish to light.

LEWIS STEVENSON.

MYASTHENIA GRAVIS

Myasthenia gravis is a disease of the muscles, particularly those of the face, the masseters, and the muscles for deglutition and speaking, which makes them fatigue very quickly. The facies is nearly always characteristic, with ptosis of one or both upper eyelids. The generally sad expression is almost pathognomonic of this condition.

Incidence.—The disease occurs in adults, as a rule, but occasionally it is seen, even in a malignant form, in young people.

Etiology.—The cause of myasthenia gravis is not known. The observation of a persistent thymus in the form of a thin sheet in some patients at autopsy, and the fact that symptoms of the disease often disappear during pregnancy, arouses suspicion of some endocrine defect.

Morbid Anatomy.—There is no constant lesion in the nervous system, but the muscles become infiltrated by small round cells ("lymphorrhage" according to Buzzard). The thymus gland persists in some cases, and lesions may also occur in the liver and thyroid gland. Developmental anomalies, such as duplication of the great toe, malformation of the aqueduct of Sylvius, etc., have at times been associated with this disease.

Symptoms.—The chief complaint is usually rapid fatigability of certain muscles. In attempting to comb the hair, for example, it becomes impossible to raise the arm above the head more than once or twice. Some individuals also cannot chew without the rapid onset of fatigue in the jaws. Speech becomes an effort, and may undergo some alteration (dysarthria); swallowing is difficult; and there may be a good deal of general weakness. Ptosis develops in one or both upper eyelids, and the face assumes a sad, sleepy appearance as the result of combined ptosis and facial diplegia. It is difficult for the patient to close the eyes tightly, and diplopia is often caused by weakness of one or the other of the extraocular muscles. Sudden attacks of dyspnea and collapse are frequent and often fatal, but the disease may run a subacute or chronic course for many years, and may even, in some cases, disappear temporarily or even permanently.

The muscles affected neither undergo atrophy nor show the reaction of degeneration. The characteristic electrical reaction, the myasthenic reaction, does, however, develop. When the muscles are stimulated by faradic current, repeated at intervals of seconds, the muscular contractions become weaker with each stimulation and soon disappear. After a short rest the muscle regains its normal excitability.

Treatment.—Adequate feeding is essential, and, in acute cases, absolute rest in bed. Tonics are useful. Electrical therapy should be avoided. The thymus has been treated with *x*-ray in many cases, but not with any marked success.

Lewis Stevenson.

LANDRY'S PARALYSIS

Definition.—Landry's paralysis is a form of acute, ascending paralysis of the spinal cord, which was first described in 1859 and is still recognized as an entity. It is usually rapidly fatal.

Incidence.—The disease attacks for the most part healthy young adults, and is frequently preceded by influenza, gonorrhea, and other infectious diseases. The author has seen it during epidemics of lethargic encephalitis; in one case except for the lack of sensory change it resembled the acute infectious neuronitis described by Kennedy.

Etiology.—The causal agent is not always the same. In some patients the condition is undoubtedly due to the virus of poliomyelitis, while in others the virus of epidemic encephalitis or of acute infectious neuronitis probably plays the etiological rôle, although this has not yet been satisfactorily demonstrated. Botulism and the paralytic form of rabies are said, at times, to produce the syndrome of Landry's paralysis. Other micrococci resembling the *Pneumococcus* have been known to cause the disease.

Morbid Anatomy.—The lesions in the *spinal cord* vary greatly in severity. In certain rapidly fatal cases they are very slight, while in others there is an extensive change resembling that of acute poliomyelitis. There may be vascular lesions in the gray matter of the cord, particularly in the anterior horns, or merely simple chromatolysis with displacement of the nucleus in the motor cells of the anterior horns.

Symptoms.—At the onset there is a feeling of malaise, slight pain in the back, and heaviness in the legs, which become weak. There may be fever at first, and sometimes myoclonic twitching of the abdominal muscles. Within a day or two the patient cannot walk because of weakness in the legs, and the paralysis spreads rapidly upward, involving the trunk, arm, respiratory, and throat musculature. The bladder and rectal sphincters are not usually involved. The mind remains clear. Deep reflexes disappear in the legs, and later in the arms. As a rule, there is no definite loss of sensation in the legs or elsewhere.

Diagnosis.—Although clinical diagnosis from the point of view of neurology is usually easy, attempts should be made to determine if possible the causal agent. Cultures from the blood and spinal fluid should be made by a pathologist who is familiar with poliomyelitis and epidemic encephalitis. Animal inoculations are desirable.

Probably the only feature which distinguishes Landry's paralysis from *ordinary acute poliomyelitis* and *acute infectious neuronitis* is its rapidly progressive course. The *acute myelitis* due to syphilis of the cord and to neoplastic invasion of the cord and meninges must also be differentiated. In these conditions the definite sensory level which can usually be discovered rises as the disease progresses upward in the cord. *Acute multiple neuritis* caused by alcohol or other toxic agents can be distinguished by taking a careful history, and by the pain in the limbs and loss of sensation in the hands and feet. The possibility of *periodic family paralysis* must be kept in mind, and should be suggested by the history of previous transient paralysis.

Prognosis.—Death has been known to result within two days and to be delayed for as much as a month, but it usually takes place within a week after onset. In rare instances, when the lesion in the cord has stopped before reaching the medulla, the paralysis has gradually disappeared within one or two years.

Treatment.—The treatment consists of administration of warm sponge-baths or packs, colonic irrigation, repeated lumbar puncture, and the exhibition of urotropin. The patient should be disturbed as little as possible.

Lewis Stevenson.

DISEASES OF THE MENINGES

Diseases of the Dura Mater (*Pachymeningitis*).—Malformations.—*Malformations of the meninges* are commonly associated with such bony defects as *spina bifida*. *Spina bifida occulta* may be accompanied by abnormal formation of the meninges. Incorporation of the roots of the cauda equina or lower portions of the spinal cord causes degeneration, chiefly of

the posterior column. Symptoms referable to this may not become manifest until adult life, and may be confused with those of such other diseases as tabes.

Disease of the dura mater itself probably produces no symptoms except some pain. Only when it leads to pressure on the brain, cord, or nerve roots is there manifested more important evidence of the disease.

Malignant growths of a sarcomatous nature may originate in the dura mater, most frequently at the base of the skull. In the early stages this produces symptoms suggestive of some chronic inflammatory condition by its implication of the cranial nerves; in advanced stages the symptoms are those of brain tumor. Malignant growths may also extend into the dura mater from such structures as the vertebræ, and produce no other symptoms than those of the bony disease until the nerve roots or the spinal cord are pressed upon. The same may be said of tuberculosis and syphilis when they involve the dura mater.

Infection.—*Tuberculosis* rarely affects the dura mater alone, although tuberculous lesions (diffuse thickening or isolated tubercles) have been seen on both the brain and spinal cord.

Syphilis not uncommonly causes chronic thickening of the dura mater, usually over the cervical region of the spinal cord. The diffuse pains in the neck, shoulders, and arms, which are characteristic of this condition, are very resistant to treatment. Pressure on the motor roots may lead to muscular atrophy. "Claw-hand" is not an uncommon deformity. Thickening over the cerebral hemispheres causes intractable headache, localizing signs such as convulsions, or evidence of general paresis.

Hemorrhage.—*Subdural hemorrhages* of apparently spontaneous origin are possibly much more common than has been suspected. The majority are probably caused by syphilis, but atrophic changes in the brain, as in senility, pregnancy, endocarditis, some of the severe anemias, hemorrhagic diathesis, and the acute infectious diseases also play an etiological rôle.

To the not uncommon subdural hemorrhages for which no cause can be found the name *Pachymeningitis interna hemorrhagica* has been given, because it is assumed that the bleeding originates in a thin, highly vascular membrane which is thought to have formed on the inner surface of the dura mater previous to the hemorrhage. It is possible that it is a result of the oozing of blood from a vessel in the leptomeninges. Evidence of this is the finding at autopsy of blood, which cannot be wiped off, incorporated in the leptomeninges; but although the blood may remain in a clot, become organized over the cerebral hemispheres, and even become ossified, this does not seem to be the usual process.

At onset the syndrome varies greatly. Many patients have sudden severe headache with dizziness, but no loss of consciousness. These symptoms, with marked stiffness of the neck, may persist for weeks without other manifestations. Prompt relief may follow lumbar puncture, and if this treatment is given every two or three days until the spinal fluid is clear, the patient may be completely restored to health under favorable conditions. Some patients, particularly the senile, suffer from great restlessness, delirium, or mania during the hemorrhage, and die from the resulting exhaustion. At times unconsciousness, which develops slowly or suddenly according to the rapidity of bleeding, is the first symptom. Focal signs, such as hemiplegia, aphasia, and visual disturbances, are probably

indications of clotting and organization over the appropriate areas, or of actual laceration of the brain tissue by the hemorrhage.

The spinal fluid may at first resemble pure arterial blood, except that it does not tend to clot. If centrifuged or allowed to settle, the supernatant fluid has a yellowish or brownish tinge. This discoloration may be considered evidence that the bleeding is not caused by a faulty lumbar puncture, since such staining cannot develop until about twenty-four hours after the manipulation. Sometimes the spinal fluid remains clear.

Diseases of the Pia Mater.—*Diseases of the Leptomeninges.*—Inflammation of the leptomeninges may be caused by other organisms than the meningococcus, tubercle bacillus, and spirochete of syphilis. As in the case of the dura mater, the infection may be introduced by trauma, extension from neighboring bony structures, or by the blood or lymph. Thrombosis of the blood sinuses may be caused by a meningitic process in the surrounding tissues, or may itself produce the meningitis.

The meningitis due to trauma or disease of the bones is more or less localized or unilateral. Significant evidence of such a condition is facial neuralgia, or paralysis of the face and eye muscles which result from involvement of the nerve supply by the exudate. The type of meningitis derived from the blood-stream frequently begins basally and produces about the same clinical manifestations, but it more often involves both hemispheres.

The *lesion* may vary in degree from a congestion and dulling of the lustre of the pia-arachnoid to a frankly purulent infiltration. At times the purulent areas are more or less discrete, especially in such crevices as the Sylvian fissure or about the cerebellum.

The constitutional diseases sometimes complicated by meningitis are endocarditis, septicemias such as those of childbirth, typhoid fever, and gonococcal infection; or any of the infectious diseases, especially pneumonia. The condition also results from such local infections as erysipelas of the scalp, face, and neck; disease of the frontal sinus or ethmoid; infection of the nose; and, most frequently of all, from disease of the middle ear. Although all types of organisms may produce the inflammation, those most commonly recovered (direct smear or culture) are the pneumococcus and streptococcus.

Symptoms and Signs.—The onset may be insidious, particularly when the primary constitutional or local disease has been severe, but it may also be fulminating when the condition develops as a complication of some other disease or as an apparently primary disturbance. The early signs are *headache*, *malaise*, *irritability*, *restlessness*, *stupor*, or *delirium*. *Vomiting*, *anorexia*, and *constipation* are other common general symptoms. *Convulsions*, *neuralgia*, and *paralyses* point clearly to the central nervous system as the site of the lesions. *Stiffness of the neck* and *Kernig's sign*, although characteristic, may be absent and are not essential for diagnosis. The *reflexes* are usually not affected, but may be somewhat increased or abolished in the more severe cases. Lumbar puncture demonstrates that the *spinal fluid* is turbid except when the condition is particularly well localized. A cell content of 1500 cells per cubic millimeter, which produces turbidity visible to the naked eye, is pathognomonic. In acute meningitis most of these cells are polymorphonuclear leukocytes. The formation of a pellicle in the cerebrospinal fluid after it has stood for several hours suggests tuberculous meningitis, but may be associated with other types of leptomeningeal

inflammation. The spinal fluid may be so purulent that it only passes with difficulty through a needle of ordinary caliber. The *white cell count of the blood* is usually high, as in other infections. The *temperature* varies according to the virulence of the infection and its curve is usually of the septic type.

Prognosis.—The prognosis is always serious. Most patients die within three or four days, but a few suffer from a more subacute condition. When the disease is caused by such local disturbances as fractures and disease of the bones of the skull, the chances of recovery are best. Occasionally death does not follow the type of leptomeningitis which complicates general infection, but this is rare. Increasing turbidity of the cerebrospinal fluid, high fever, delirium, inanition, and evidence of progressive exhaustion are of bad prognostic import.

Residual defects, like mental abnormalities, paralyses, and other manifestations of permanent damage to the nervous tissues, are uncommon.

Treatment is largely symptomatic. Such local lesions as fractures and diseases of the skull, of course, demand appropriate therapy. *Repeated lumbar puncture* relieves pressure, draws off infected material, and often gives much subjective comfort. Daily puncture and removal of 10 to 20 c.c. of spinal fluid may be more efficacious than less frequent and more drastic drainage. *Hot packs* and *prolonged warm baths* have a marked sedative effect. Some physicians advocate the use of *counter-irritation* by means of mustard plasters or even of the actual cautery along the spine. *Saline purges* relieve intracranial pressure and eliminate toxins. *Urotropin* may be administered in large quantities, and *mercury* has been given, but with questionable result.

Robert G. Armour.

MENINGO-MYELO-ENCEPHALITIS

ACUTE ANTERIOR POLIOMYELITIS

(*Infantile Paralysis*)

Definition.—Acute anterior poliomyelitis is an acute, general, systemic infectious disease which tends to involve the central nervous system, attacking especially the gray matter of the spinal cord, but capable of producing widely scattered lesions throughout all the tissues of the brain and cord.

Clinically the disease is characterized by two definite phases: the first, a stage of general toxemia; the second, a manifestation of the results of damage to the ganglion cells of the anterior horns and the ganglia of the posterior roots. The disease often occurs sporadically, but has strong epidemic propensities.

History.—The disease is ancient, and was probably first described with any degree of accuracy by the English physician Underwood in 1774. The first systematic study of a large group of cases which finally established the disease as a clinical entity was published by Jacob von Heine in 1840 in Kolmar, Germany. He undoubtedly recognized that there was a febrile period preceding the onset of paralysis. Since Heine's time there have been

many contributions to the literature, notably by Strümpell, Medin in Sweden, whose name is often associated with that of Heine, Wickman, Flexner, Amoss, and others. The first successful transfer of the disease to monkeys was accomplished by Landsteiner and Popper in Vienna in 1909, and in the same year Flexner and Lewis succeeded in establishing the disease definitely in the monkey and carrying it from generation to generation. Very shortly after this the virus was shown to be filtrable. In 1914 Flexner and Noguchi reported experiments on the isolation and cultivation of an organism which seemed always to be associated with the disease. The etiological rôle of this organism has not yet been broadly confirmed or discredited by other observers. Rosenow has also reported the presence of a form of streptococcus which he believes to be the etiological agent of the disease.

Etiology.—Not until the last decade has anterior poliomyelitis been definitely attributed to the presence of a micro-organism, but there seems now to be little doubt that the disease is infectious and is transmitted from person to person. Boys are somewhat more affected than girls (in some epidemics 56 to 44 per cent.), and children appear to be most susceptible during the second year of age. Those between three and seven years old are next in order of susceptibility; and among older children the incidence falls rapidly until it reaches almost zero at twenty years of age. Recently, however, the disease has attacked adults more often than formerly. It is possible to recognize the type of individual who is particularly susceptible to the infecting agent. Some attempts have been made to describe the morphological characteristics of a type of patient very often afflicted with the disease. In the epidemic of 1916 a type of child frequently attacked was large, well grown, and plump, with certain characteristics of face and jaws, broad brows, and round face. The adolescents and young adults who acquired poliomyelitis also seemed to be physically similar. For instance, the arrangement of the maxillæ showed a slight prognathism, the features being rather sharp and pointed and the teeth crowded; and there were many small pigmented moles over the neck and face. All of these observations seemed to indicate that an important element in the etiology of the disease is the special susceptibility of certain individuals.

Bacteriology.—There is no question that from the tissues of the spinal cord and brain of human beings and monkeys who have died of the disease it is possible to obtain a filtrate which is capable of producing the infection in other animals.

An organism described and grown by Flexner and Noguchi in an artificial medium has been found to reproduce the disease in animals, thus fulfiling Koch's law. So far, however, this work has not been confirmed by other observers. One of the most important reasons for believing that this organism is the specific agent is the fact that it is neutralized by the serum of convalescent animals, just as the virus filtrate is neutralized by such a serum. The polymorphous streptococcus, described by Rosenow and Nuzum, cannot be so neutralized.

Epidemiology.—Up to within a few years ago there was a very definite relationship between the epidemics of this disease and warm weather, but apparently, since poliomyelitis has spread throughout the world, this has become less marked, and there have been a number of winter epidemics. Nevertheless, there does seem to be a greater tendency for the virus to be active, or the children to be more susceptible, during the summer months. In 1907 Wickman showed by a fine series of epidemiological studies that the disease was transmitted from person to person. Wickman also recognized that the so-called abortive type, which never developed into paralysis,

was a definite link in the chain of development of the epidemic, and that apparently healthy persons might be carriers; while Shepherd showed how the indirect contact of apparently healthy individuals might be responsible for transmission of the disease. So far the burden of proof lies with those who believe in an insect carrier. The mass of evidence for direct transmission is now almost too great to be overthrown. The incubation period of poliomyelitis is from four to seven days.

Morbid Anatomy.—As a result of observations on monkeys, it has been shown that the virus is widely distributed in the body. Not only is it present in lymph-nodes, tonsils, and pharyngeal mucosa, but in the spleen, bone-marrow, and mesenteric lymph-nodes, and in the posterior ganglia of the spinal roots. It has never been detected in the spinal fluid nor in the blood of man. In the experimental disease the virus disappears from the blood within seventy-two hours after the injection of the animal. The changes in the tissues of human beings outside of the central nervous system are very extensive. They usually include hyperplasia of the lymphatic glands, of the spleen, and of the intestinal lymphatic nodes. Furthermore, there is often interstitial small cell infiltration of the portal spaces of the liver, with general cloudy swelling of all the parenchymatous organs. In the central nervous system the lesion is much more specific. The meninges of the cord and medulla undergo, as a rule, mononuclear infiltration around the blood-vessels which enter the fissures of the cord. The cellular invasion about the vessels within the lymphatics is heavy and often nodular. The spinal cord develops the most pronounced lesions in the anterior gray matter. These are of three different types, vascular, interstitial, and parenchymatous. When the anterior horn-cells become necrotic they are commonly invaded by phagocytes—so-called neurophages. There are often hemorrhages about the affected areas in the cord.

Microscopically, the earliest change that can be seen is a perivascular infiltration of small round cells along the blood-vessels of the leptomeninges. The virus, according to the findings of the experimental disease, is suspended in the spinal fluid and thus conveyed along the perivascular lymph-spaces, and along the extension of these spaces, causing the characteristic small round-cell reaction. The outpouring of these cells may be so great as to choke the spaces and bring pressure to bear upon the encircled blood-vessels. The process spreads from the parietal meninges and enters the interior of the cord by the anterior fissure along the branches of the anterior spinal artery. The engorged vessels of the pia frequently rupture and there is a generalized edema. Besides the interstitial reaction, the cellular infiltration, hemorrhage, and edema, which exert pressure upon the cells of the anterior horn, there appear definite changes in the ganglion cells themselves. The probability is that all the adverse forces, mechanical and toxic, are at work, so that the anterior horn-cells are both poisoned and strangled to death.

Symptoms.—There seems to be little doubt now that the clinical picture of so-called abortive anterior poliomyelitis and the preparalytic febrile stage of the paralytic type are one and the same thing. It is for this reason that the existing classifications, which are based upon the position of the lesion in the cord, do not convey a correct impression of the nature of the disease. It is probably more correct to consider this malady an acute, general, systemic disease in which the paralysis is incidental. The *prodromal*

symptoms vary to some extent in different epidemics. The febrile reaction may be associated either with a coryza or cough, or with a violent gastro-intestinal disturbance, usually a diarrhea and very often vomiting, or simply general malaise and loss of appetite. In addition to these classical symptoms of a febrile disturbance the child assumes a peculiar attitude: becomes restless and somnolent by turns, and is exceedingly irritable when aroused or handled. The expression of the eyes is often that of a hunted animal. Physical signs at this stage are not definite except for the fact that the child is very frequently unwilling to flex the neck anteriorly, probably because inflammation of the posterior spinal root ganglia makes this painful. In executing the Kernig manipulation the spine is flexed anteriorly, and what happens to be a reflex spasticity in neck and thigh is actually almost always a voluntary resistance on the part of the child. This probably explains also why children in this early stage so frequently lie on the side or in marked opisthotonos.

Following the acute febrile stage there may be a disappearance of the diarrhea and all other symptoms for a period of twelve, thirty-six, or forty-eight hours. The child then suddenly becomes ill again; headache is marked and paralysis develops. In many cases there is no such intermission and the febrile phase changes immediately into the paralytic. Careful questioning, however, in these cases often reveals the fact that one or two days previously there has been a slight digestive disturbance.

The *reflexes* are most erratic. At times no change appears, but they may be highly exaggerated or unequal. Not infrequently the tendon reflex disappears, portending paralysis, only to reappear again in a few hours. It is striking that during the acute stage of the disease diarrhea is very common, but that as the disease advances to the paralytic stage constipation supervenes.

The *fever* of acute poliomyelitis is usually of short duration; the temperature rarely rises much higher than 102° to 103.5° F., and falls rapidly within twenty-four to forty-eight hours. The *superficial lymph-nodes* are invariably palpable and almost always enlarged. The *blood*, during the first phases of the disease, shows a moderate leukocytosis and the number of polymorphonuclear cells averages 15 per cent. above normal. There is a considerable reduction in the lymphocyte count.

The *spinal fluid* in the early hours is clear under increased pressure and contains no cells. Occasionally *globulin* appears. Later, should the disease develop into the second or meningeal stage, the character of the fluid changes: the cell count rises, but the quantity and pressure of the fluid diminish. The presence of more than 10 cells per cubic centimeter is abnormal, but in some cases the count may be as high as 2500. At first the cells are multilobular; but at the end of twenty-four to thirty-six hours, when the globulin content begins to rise, they are for the most part small mononuclears. Generally speaking, if the count is lower than 100 in the first twelve to eighteen hours, paralysis is less likely to develop than when the count is 500 or more. In one type of case with profound stupor, resembling that of tuberculous meningitis, the count runs below 100, and the course is invariably mild; facial paralysis, however, frequently develops. If lumbar punctures are made at ten- to twelve-hour intervals in suspicious cases, it is often possible to note the time of meningeal invasion. The fluid of acute poliomyelitis is rarely turbid because the cell count is hardly ever

high. This fact is sometimes of value in differentiating this disease from cerebrospinal meningitis. Spinal fluid from patients with poliomyelitis may be differentiated from that characteristic of tuberculous meningitis by absence of the delicate gray "Welsbach mantle" clot, by its reduction of Fehling's solution, and by the absence of *tubercle bacilli*.

Paralysis.—The paralysis appears with the greatest frequency on the second day. As a rule, the initial paralysis represents the final extent to which it is likely to go. Because the lesion may vary from slight irritation of the meninges to complete destruction of the entire gray matter of the cord, the variety and extent of the paralysis is enormous.

First of all the lesion may very occasionally involve the upper motor neuron and so give rise to the so-called spastic or cerebral type of Strümpell. The great majority of paralyzed cases, however, fall into the group in which there is involvement of the lower motor neuron. Statistical studies reported by Wichman of the distribution of paralysis in this group show the following figures. The figures are from a series of 868 cases seen by him in 1905:

1. One or both legs	353
2. One or both arms	75
3. Combination of arms and legs	152
4. Combination of legs and trunk muscles	85
5. Combination of arms and trunk muscles	10
6. Trunk muscles alone	9
7. Paralysis of "the whole body"	23
8. Ascending paralysis	32
9. Descending paralysis	13
10. Combination of spinal and cranial nerves	34
11. Cranial nerves alone	22
12. Localization of paralyses not given	60

The distribution and location of paralysis appears to follow no law. The palsies are usually flaccid and affect individual muscle groups of spinal segmental distribution. Atrophy is the rule, and depression or loss of abdominal and deep reflexes almost constant. Objective sensory losses are almost unknown, and sphincter disturbance except in the earliest stages is rare.

Treatment.—At present the most important question under discussion in the treatment of acute poliomyelitis is whether or not any *serum* is effective. The evidence obtained from neutralization experiments *in vitro* and from the protection of monkeys by means of convalescent serum and from the numerous observations of Netter, Amoss, Ayer, Draper, and others, it would seem that it is not only justifiable but desirable, to administer the serum of convalescent or cured patients intraspinally and intravenously. After the paralysis has appeared, administration of serum is unavailing. If a preparalytic diagnosis can be *made*, however, especially within twelve to eighteen hours of the onset of symptoms, 15 c.c. of convalescent serum should be given intraspinally, and if possible as much as 100 c.c., intravenously. It is still difficult to accept as a specific agent the serum prepared by Rosenow from horses injected with the polymorphous streptococcus, particularly as this serum does not neutralize the virus.

The therapeutic measures usually employed for any acute infection should be instituted, and, as irritation of the central nervous system develops, everything should be done to keep the child as quiet as possible.

The treatment of the paralysis may be divided roughly into two types: treatment during the early hours and days of its appearance, and the

subsequent management of the permanent paralysis. In the first, much damage may be done to paralyzed patients by energetic treatment. It is far better to err on the side of inaction than to begin massage and passive motion too soon. Above all things the use of electricity should be avoided at this stage. As soon as the child will permit it, massage and general passive exercise should be begun. From the very beginning care should be taken to prevent the contractures which develop so quickly. If treatment has been properly carried out in the first two to three months there should be no crippling deformity. The tendency to recovery is surprisingly great even when a limb is completely flaccid.

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EPIDEMIC ENCEPHALITIS

(Encephalitis Lethargica, Epidemic Neuraxitis, Epidemic Meningo-encephalo-myelo-neuritis, Epidemic Stupor)

Definition.—Epidemic encephalitis is an epidemic, toxi-infectious malady, causing both diffuse degenerative and disseminated inflammatory changes in the central nervous system and its coverings, characterized clinically by a marked diversity of symptoms in different cases and in successive stages of the same case, partly because of variations in the intensity of the intoxication, partly because of differences in localization of the scattered inflammatory foci. Somnolent-ophthalmoplegic, Parkinson-like, hyperkinetic, and psychotic syndromes are the commoner manifestations; meningeal, apoplectic, epileptiform, tabetic, and poliomyelitic symptom-complexes are occasionally observable; and *formes frustes* and aberrant types are numerous.

History.—The disease is probably not a new malady, though it has become generally known to the profession only since the present pandemic broke out in the winter of 1916–17. von Economo carefully described the disease at that time and called it "lethargic encephalitis"—a misnomer, since it is the patient rather than the encephalitis that is lethargic. The "nona" in the early nineties of the last century, the "sleeping sickness," and ophthalmoplegia that were observed during the influenza epidemic of 1712 may have been the same disease. Even the present pandemic may have begun before 1916, since Cruchet in Bordeaux states that he observed cases as early as 1915. During 1917 an epidemic occurred in Australia, reported by Breinl as a "mysterious disease"; von Economo believes that it was epidemic encephalitis. In 1918 encephalitis became prevalent in

France, Netter recognizing it as an "Encéphalite lethargique épidémique," and in the spring of the same year the disease was met with in epidemic form in fifty-one sanitary districts in England. In Baltimore the first case, a patient from Marion, S. C., was seen in February, 1919. Bassoe reported cases in Chicago in March, 1919, and about the same time the malady began to appear in and to be reported from various parts of the United States and Canada. In the first Vienna epidemic (1916–17) the prevailing type (as in the epidemic in France in 1918) was the somnolent-ophthalmoplegic, though there were also examples of the Parkinson-like, the hyperkinetic, and the psychotic syndromes. In the Australian epidemic (1918) the poliomyelitic type predominated and the disease was at first erroneously supposed to be poliomyelitis. In the English epidemic of the same year, bulbar paralytic types were common (at first supposed to be botulism), as were also Parkinson-like and catatonic types (hence the name "epidemic stupor"). In the epidemic in Germany in 1919 the choreatic type, the Parkinson-like type, and the tabetiform type (with pupillary disturbances, hypotonia, and areflexia) were described. In the great epidemic that began in Italy in 1919–20 and spread over Austria and Germany, the hyperkinetic-myelitic forms (choreatic, myoclonic) predominated. Here in America a great variety of types have been encountered; though the somnolent-ophthalmoplegic were more abundant at first, later on the cases which were characterized by Parkinson-like and hyperkinetic syndromes were more frequently seen. The disease appears to be increasing markedly in prevalence in the United States, judging from the deaths reported in the registration area of the Bureau of the Census.

Incidence.—How the virus of epidemic encephalitis is transmitted is unknown, though it has been assumed that the nasopharynx is the portal of entry. In favor of the idea of contact infection is the fact that the incidence among physicians has been exceptionally high. Though instances of house infection, of conjugal infection, or of spread from one person to his family or close companions have been few, some have been reported. Thus, epidemic outbursts of intense contagion have occurred in England in institutions for young females, and several children born of parents suffering from the disease have become infected. No *age* is exempt. Incidence appears to be greatest, however, between twenty-five and forty-five years of age, thus differing from the Heine-Medin disease in which 90 per cent. of those affected are children under ten years of age.

Epidemic encephalitis is commonest during the *winter months*, but new cases may occur at any time of year. About three *males* are attacked to two females. *Occupation* appears to exert no special influence in etiology. *Racial factors* may be of some import, since the incidence among foreign-born adults in New York City was relatively higher than in the native population (Wechsler); and in Warsaw the Jews were more often attacked than the Christian population (Sterling).

Etiology.—That epidemic encephalitis is an infectious disease due to invasion of the body by a living micro-organism seems certain, and many attempts have been made to discover and to grow the infective agent. Wiesner (1917) reported the isolation of a Gram-positive bacterium that he called *Diplostreptococcus pleomorphus*. Loewe and Strauss grew in Noguchi's tissue-ascitic-fluid medium a minute filtrable Gram-positive coccus that appeared in diplo-forms, chains, and clumps, an organism that closely resembled that grown by Flexner and Noguchi from poliomyelitic material. Flexner in his "Packard Lecture" (1923) concludes that the cause of epidemic encephalitis has not yet been discovered.

The relations of the etiological agent of epidemic encephalitis to those of influenza, poliomyelitis, and herpes have been much discussed, but as yet they are far from clear.

Morbid Anatomy.—On macroscopical examination of the nervous system at autopsy, areas of hyperemia in the meninges may be seen, the vessels on the surface of the brain are engorged, and, on section, the vessels appear

prominent, especially in the basal ganglia, midbrain, and pons, where minute hemorrhages are sometimes visible (J. B. Ayer). On microscopical examination two changes can be made out: one diffuse toxic and degenerative, the other inflammatory and infiltrative. One or the other predominates according to the stage of the disease at the time of death (von Economo). The *toxic-degenerative process* manifests itself as a diffuse edema, hyperemia, increase of the glia nuclei along the vessels, and indistinct staining of the tigroid substance in the nerve-cells. The *inflammatory change* appears as scattered patches of infiltration, especially in the gray matter, with accumulation of small and large mononuclear cells and plasma cells in the sheaths of the vessels and in the perivascular spaces. The nervous tissues themselves show also patches of diffuse infiltration with the same types of cells; and there are signs of neuronophagia. Proliferation of the glia-cells can be seen in the inflammatory areas.

The inflammatory foci tend to be most abundant in the brain-stem (basal ganglia, midbrain, and pons). However, in the epidemic in Australia in 1920, in which hyperkinetic-myelitic forms predominated, the cerebral cortex and the basal ganglia were relatively free from lesions, whereas inflammatory foci were numerous in the midbrain, pons, medulla, and spinal cord (especially in the anterior horns). In chronic relapsing cases, lesions of different ages have been demonstrable at autopsy. The pathological histology of American cases has been carefully studied and reported in papers by Ayer, by Bassoe, and by Spiller. Evidences of toxic changes outside the nervous system (serous membranes, kidneys) observed by Boyd of Winnipeg indicate that the disease must be regarded as a general infection with special localization in the central nervous system. It has been suggested that the disease first attacks a mucous membrane (naso-pharynx, conjunctiva, gastro-intestinal mucosa) and then extends along the perineural lymph channels to the central nervous system (Abrahamson), but proof of this view remains to be obtained.

The *incubation period* is believed to be about two weeks.

Symptoms.—The *onset* may be either sudden or gradual. The mode of onset has varied markedly not only in different epidemics, but also among cases in the same epidemic. The first symptoms may be those of an acute respiratory infection, with headache, malaise, and fever. In the Vienna epidemic of 1916-17 there was usually a forestage with symptoms of slight meningeal irritation before the somnolence and eye-muscle paralysis appeared. In the United States the onset in some cases was sudden, with severe pains in the head, fever, and delirium; in other cases it was more insidious, with fever, diplopia, and slight mental confusion; or with sensory disturbances and pareses in cerebral nerve domains. In a few cases the disease has been ushered in by a stroke of apoplexy, an epileptiform attack or sudden syncope, or a severe vertigo.

The clinical picture of *the fully developed disease* varies greatly. A large number and variety of symptoms may be met with in the most diverse combination and sequence. As Achard puts it, "the disease is polymorphous and acyclic." Experience with many cases indicates that the manifestations may simulate those of almost every well-known neurological symptom-complex, thus making differential diagnosis sometimes very difficult. Certain syndromes, however, are more common than others and merit especial mention.

Lethargic or Somnolent-ophthalmoplegic Type.—A triad of symptoms—fever, somnolence, and ophthalmoplegia—characterizes the lethargic type of encephalitis. After a brief initial stage with fever (of variable degree) and symptoms of meningeal irritation, the patient becomes drowsy and exhibits eye-muscle paralysis. Sometimes there are other symptoms—general rigidity, paralyses in the limbs or head, symptoms of motor irritation, and delirium, or other mental disturbances. The fever may be slight or severe; many afebrile cases have been noted.

Parkinson-like Type.—After a vague onset with headache, fever, and other symptoms often erroneously thought to be due to influenza, the syndrome of *Paralysis agitans* (usually without tremor) develops. The facial mask, the abnormal rigidity of the trunk and limbs, the monotonous voice, the micrographia, the tendency to propulsion, and festination are symptoms quite like those seen in Parkinson's disease, but in encephalitis their sudden appearance and the absence, as a rule, of the "pill-rolling" tremor are striking points of difference. Some of the patients exhibit "*palilalia*" (repetition of words or sentences in ever-increasing tempo). The Parkinson-like forms of epidemic encephalitis are believed to be due to lesions of the *Globus pallidus* (pallidal system of Ramsay Hunt).

Hyperkinetic Types.—In the hyperkinetic type, following an initial stage of fever and excitement, severe symptoms of motor irritation appear, in the form either of choreatic (or choreo-athetotic) movements or of myoclonic contractions. In the *choreiform* variety there are involuntary and irregular movements of the automatic associated type; these may be general, unilateral, or local in distribution, and may vary much in intensity. Occasionally the movements of an extremity are slow and rhythmical, recurring regularly eighteen or twenty times per minute ("bradykinetic oscillation" of Marie and Levy). The choreiform types are believed to be caused by lesions of the neostriatal system of neurones (Ramsay Hunt). In the *myoclonic* variety there is marked, irregular twitching of muscles or parts of muscles, probably due to irritative lesions in the spinal cord. Bilateral twitching of the abdominal muscles may be an early sign of encephalitis (T. F. Reilly). Less common is a "bilateral synchronous myoclonia," during which the muscles of the trunk and of the proximal portions of the extremities contract fifty or sixty times per minute (Hamill).

Psychotic Types.—Psychoses of the "organic reaction type" may dominate the clinical picture in epidemic encephalitis. Mental grasp is impaired; memory defects are evident; orientation as to time, place, and persons is faulty; and attention is disordered (Kirby). In the more acute forms active delirium may alternate with pathological drowsiness or stupor. Emotional disturbances are common and tend to be persistent. In some cases marked mental deterioration occurs and may be mistaken for general paresis. Manic and melancholic states have been observed, and less often a condition simulating dementia præcox has been seen. In children there may be marked alterations of character and oddities of behavior (Hohman). Many patients are drowsy in the daytime, but remain wide awake and alert through the night. Psychoneurotic states are common as sequels of epidemic encephalitis and are often very resistant to therapeusis.

Other Types.—Many other types have been described, including (1) a poliomyelitic type (with lower motor neuron paralyses), (2) a posterior root ganglion type (with herpes and radicular neuralgias or anesthesias),

(3) a tabetic type (with ataxia and sluggish pupils, even with Argyll Robertson pupils), (4) an epilepto-maniacal type, and (5) a cataleptic type (with statuesque attitudes).

Aberrant Forms and "Formes Frustes."—Very peculiar aberrant forms of the disease may occur which simulate some other malady, often of some part of the body other than the nervous system. Examples of such aberrant forms are (1) the intestinal types (Massari), (2) the dyspneic types (von Economo), and (3) the fulminant cases that terminate fatally after a few hours (*Encephalitis siderans*). In one case, observed by Barker and Sprunt, tetany developed as the result of a postencephalitic paroxysmal hyperpnea. Abortive forms and *formes frustes* are undoubtedly very common when the disease is epidemic; nuclear paralyses in the domain of the cerebral nerves, radicular neuralgias, deafness, vertigo, and trismus may be the only manifestations. Reasoning from our knowledge of other infections, it is probable that healthy virus-carriers are not uncommon, though as yet proof of this is lacking.

Diagnosis.—When the disease is epidemic and typical cases are occurring, encephalitis should always be suspected in puzzling cases of fever, somnolence, or delirium. In no other condition, perhaps, is a thorough general diagnostic study, inclusive of neurological and psychiatric analysis, more important for correct diagnosis than in epidemic encephalitis. Signs of meningeal irritation, external or internal ophthalmoplegia, neuralgias or paralyses in cerebral nerve domains, or pathological drowsiness associated with fever or leukocytosis should always excite suspicion. On lumbar puncture the cerebrospinal fluid may be normal, but often there is an increase in the globulin content, a slight increase in the cell count, and an increase in the sugar content (hyperglycorachia), changes that are strongly corroborative of encephalitis when the Wassermann reaction is negative.

Among the conditions to be differentiated from epidemic encephalitis are: (1) botulism, (2) nervous forms of influenza, (3) epidemic cerebrospinal meningitis, (4) tuberculous meningitis, (5) uremia, (6) vascular lesions in the nervous system, such as cerebral hemorrhage, embolism, or thrombosis, (7) cerebrospinal lues and paralues, (8) brain tumor, (9) Heine-Medin disease, (10) multiple neuritis, and (11) multiple sclerosis.

Prognosis.—The mortality varies in different epidemics. It probably amounts to 20 or 30 per cent., if the outspoken cases only are considered; the death rate would doubtless be lower if atypical and rudimentary cases were to be included. Of those who survive the acute stage of the illness (four to eight weeks), perhaps 10 per cent. develop a progressive disease of the central nervous system (Grossman). Persistent insomnias, mental impairment, psychoneurotic states, tremors, irregular involuntary movements, autonomic disturbances (pupillary anomalies, sialorrhea, tachypnea, paroxysmal hyperpnea, cardiac arhythmias, sweats, sphincter disturbances), oddities of behavior, and Parkinson-like syndromes are common and troublesome sequels. A large proportion of the patients recover rapidly after the acute illness; others remain more or less invalid for from six months to two years, and then recover, but many patients are permanently disabled because of the residuals or sequels of the disease.

Treatment.—In the acute stage, rest in bed, isolation, protection from avoidable optic, acoustic, and tactile stimuli, skilful nursing, restriction to a liquid diet, and tepid sponging are beneficial. Lumbar puncture repeated

twice a week or oftener will frequently relieve the headache and diminish drowsiness of the early stages, especially when the pressure of the cerebrospinal fluid is increased. Water should be given freely by mouth, or by continuous *Murphy drip* if the patient be difficult to arouse. For the noctural restlessness the bromids or barbital in hot milk may be useful. In the hyperkinetic states and in violent deliria sedatives are required (bromid and chloral, or paraldehyd, by mouth; or Schlesinger's solution by hypodermic injection). No satisfactory *specific treatment* of the disease is as yet available, though some benefit may be derived perhaps from injections of serum from convalescents. Some have reported beneficial results from the administration of Rosenow's serum.

After the acute stage is over great care should be exercised to avoid relapses. Convalescents should be closely watched and their activities directed meticulously for a long time.

The therapeutic resources of the physician will be severely taxed in the management of patients suffering from residuals and sequels of encephalitis. Insomnia, asthenia, paralyses, and Parkinsonian-like symptoms are prone to persist. For the asthenia general upbuilding measures are helpful; some patients seem to be benefited by adrenal residue (5 to 10 minims after each meal). For tremor and for Parkinsonian rigidity, small doses of hyoscin hydrobromate (1/400 to 1/150 grain) are valuable. To promote recovery from paralyses, massage and galvanism may be employed. Patients with severe psychotic symptoms or exhibiting anomalies of behavior may have to be cared for, temporarily or permanently, in a closed institution.

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MYELITIS

Definition.—The clinical disturbances which in the past have been called myelitis are due to abnormal structure or function of the spinal cord of varied origin; but as clinical knowledge has increased and the understanding of the pathology of the nervous system has become more complete, the term myelitis has been used in a more restricted sense. It now refers to diffuse involvement of the spinal cord by processes of inflammation and softening. The impairment of function caused by hemorrhage into the spinal canal or medulla, vertebral disease, tumors of the spinal cord or meninges, softening from simple vascular disease, and degenerative involve-

ment of the long tracts (as in tabes dorsalis and the various scleroses) are no longer classified as myelitis. In short, the term now refers to pathological processes and clinical conditions which are the result of trauma, infection, and certain poisons or toxins.

Incidence.—The syndrome now known as myelitis is not common. In general hospitals about one patient in two hundred suffers from involvement of the central nervous system which is limited to the spinal cord. In 130 consecutive cases of such disease seen at Bellevue Hospital, there were 19 cases of myelitis due to infections or toxins. In 7 other instances trauma produced injury to the spinal cord which on clinical or *postmortem* examination proved to be myelitis. In the 11 instances in which trauma had crushed the spinal cord, the condition was considered as the result of compression of the spinal cord. Of the cases due to infection or intoxication, 8 represented chronic degenerative or subacute exudative forms of syphilis.

Etiology.—The causes of myelitis are infection, poisons and toxins, and trauma. If one excludes uncommon instances of poliomyelitis in which the fiber tracts and posterior horns are involved, and cases of epidemic encephalitis limited to the spinal cord, it can be said that there is no primary form of *infective myelitis*. The list of diseases in which secondary involvement of the spinal cord may occur is long: syphilis, influenza, tuberculosis, typhoid fever, diphtheria, and gonorrhea are the most common. In cerebrospinal meningitis, there is frequently some concomitant involvement of the spinal marrow, but clinical diagnosis during the acute stages is seldom made. Typhus, dysentery, pneumonia, measles, smallpox, and scarlet fever have been reported as the primary sources of infection. In carbuncles and in chronic infections of the kidney, bladder, and pelvic organs, lymphogenous extension to the spinal cord may occur. Direct extension from empyema has been reported. Embolism in septicemia and endocarditis may be responsible for myelitis. *Toxic myelitis* may be due to poison by carbon monoxide, carbon bisulphid, chloroform, and gasoline fumes. In cachectic states and severe anemia the spinal cord may be affected. Myelitis is not uncommon during pregnancy and the puerperium. Whether the condition associated with puerperium is toxic or due to a mild infection may be impossible to determine. *Traumatic myelitis* may be the result of direct or indirect violence. Electrical shock and the penetrating wounds made by firearms or stabbing produce local injury to the spinal cord and not myelitis of the type here considered.

Morbid Anatomy.—In the *acute stage*, gross examination reveals a swollen, somewhat soft, and injected cord. On cross-section it may be difficult to distinguish the gray and white matter because of the hyperemia, although in acute traumatic myelitis the cord may appear normal. Microscopic examination reveals three abnormalities, vascular, inflammatory, and degenerative, which vary in proportion and degree with the etiology. Edema and hemorrhages from the capillaries follow trauma and infection. Round-cell infiltration in and outside the vessel walls and glial proliferation are noticeable only in infectious myelitis. Toxic myelitis is characterized by edema and mild primary degenerative changes in the cells and myelin sheaths, and by the absence of vascular reaction. In luetic conditions vascular degeneration is prominent and endarteritis is sufficiently well developed to prove that it existed before symptoms appeared. There is also some edema with degenerative change in the cells and nerve-fibers,

and usually more or less productive inflammation of granulomatous nature. In acute traumatic myelitis an acute primary degeneration with some vascular reaction is characteristic.

In *chronic myelitis* the cord is usually shrunken, soft, and pale. Brownish pigmented spots may be seen when there has been a pre-existing acute stage with marked hemorrhagic reaction or hyperemia. In luetic cases the pia is opaque. When trauma has been the cause there are frequently fine adhesions between the meninges and marrow, with calcified areas in the pia. Microscopic examination reveals secondary degeneration with segmentation of the myelin and a progressive granular disintegration of the axis-cylinders. Proliferation of the ependyma and glia, and small cavities caused by necrosis develop and there is cellular atrophy. Distention of the perivascular spaces with granular debris is especially prominent when there has been pre-existing inflammatory exudation. Endarteritis is characteristic in syphilis.

Symptoms.—Acute Myelitis.—Infectious myelitis is usually rapid in onset, and may be apoplectiform. The constitutional symptoms which are usually present vary in severity. Paresthesiæ, slight weakness limited to one or more extremities, root pains, and disturbances of sphincter function are common prodromata. When the condition is the result of syphilis, however, symptoms usually develop gradually. In cases due to poisons and toxins either mode of onset may occur. When trauma is causal, symptoms appear immediately.

The symptoms referable to the spinal cord depend less on the cause than on the level of the involvement and the intensity of the pathological processes. Even disseminated or extensive lesions often evoke a symptom-complex referable only to one level of the spinal cord, except when the cranial nerves are involved, when the progress of the disease is gradual, or when the cervical and lumbar enlargements are both seriously affected.

Divisions of the Spinal Cord.—For convenient description, the spinal cord may be divided into three levels, each of which produces a more or less distinct syndrome; the cervical, the dorsal, and the lumbosacral which includes the cauda equina and conus. Symptoms are referable to impaired function of the various cell groups and fiber tracts and may be classed as motor, sensory, reflex, visceral, and trophic in nature. Some degree of paralysis and alteration of the tendon and superficial reflexes are prominent and present in all cases. The other symptoms are more variable and may be present in mild degree only.

1. *Cervical Cord.*—When the cervical region of the spinal cord is affected, the symptoms can be classified as follows:

Motor paralysis involves all the extremities. The arms may be affected incompletely and unequally, and the paralysis may be hemiplegic in distribution. When the onset is rapid and if the damage to the spinal cord is severe, the paralysis is at first flaccid. That of the arms is of lower neurone type and if recovery is not complete, atrophy and contractures may develop with reaction of degeneration in the affected muscles. High cervical myelitis is rare and always leads to death within a few days. When the lesion is at the level of the fifth and sixth cervical segments, the arms are frequently held semiflexed across the chest. In milder cases, and as improvement appears, the lower extremities become spastic. Flexion contracture of the legs with atrophy is an end-result when the spinal cord is

seriously damaged. Paralysis of the cervical sympathetic which produces miosis and enophthalmos is frequent. Hyperkinetic phenomena are common. They include fibrillary tremors in the arms, and automatic movements of the legs. Myoclonus is rare.

Sensory disturbances are usually less severe than motor. Hyperesthesia, paresthesiæ, and root pain in the segments involved are common prodromal manifestations which may persist. Below the segments involved there is partial or complete impairment of sensation. The type and distribution of sensory loss depend on the tracts affected, and the intensity of the lesions. Diminution of pain and temperature sensibility results from involvement of the spinothalmic tract and is most marked in severe involvement of the central portion of the spinal medulla. Deep sensibility, which includes the vibratory and position senses, is usually but little impaired. It may be the earliest to return to normal.

Reflex.—With the onset of acute and severe myelitis, all reflexes are usually lost, although at times in the earliest stages all are exaggerated for a brief period. The abdominal and anal reflexes may be retained for a day or two, and the anal reflexes may be the only evidence that functional blocking of the spinal cord is incomplete. With improvement, the tendon reflexes return in the lower extremities, the plantar responses become extensor in type, and the confirmatory evidences of the Babinski phenomenon may be found. In complete recovery, the abdominal and cremasteric reflexes are usually the last to resume normal activity.

Visceral.—Among the visceral symptoms is retention of urine and feces with loss of bladder and rectal sensation. Priapism is frequent. It may be spontaneous, or induced by catheterization or cleansing of the parts. After a varying period, usually about a fortnight, the bladder becomes automatic and empties itself periodically. Sphincter function as a rule returns early. Permanent impotence may follow even mild myelitis.

Trophic.—In severe cases prevention of decubitus is almost impossible. Edema of the paralyzed extremities and abnormalities of sweat secretion may occur.

2. *Dorsal Cord.*—The dorsal region of the cord is most apt to be attacked by the subacute or chronic forms of myelitis. The symptoms of its involvement are the same as those of cervical myelitis, except that the arms are not involved. The patient may complain of paresthesiæ in the upper extremities when otherwise there is no sensory disturbance higher than, for example, the sixth dorsal segment. This symptom may be important in establishing the disseminated nature of the disease. The upper abdominal reflexes are retained when the lesion is below the eighth dorsal segment.

3. *Lumbar Cord and Conus.*—When the lumbar region and conus are attacked the paralysis, which is confined to the legs, is flaccid in type and the paralyzed muscles atrophy. Both knee- and ankle-jerks are absent when the lesion affects the upper lumbar segments. If the level of involvement is at the fifth lumbar and first sacral segment, only the ankle jerks and the biceps femoris jerks are lost. The plantar reflex is almost always abolished. Incontinence results from paralysis of bladder and rectum.

Chronic Myelitis.—When the onset of chronic myelitis is gradual, the patient complains chiefly of weakness. This consists of heaviness and stiffness of the lower extremities when the dorsal cord is affected.

Paresthesiæ may also develop in the legs, and a girdle sensation or even lancinating pains corresponding to the segment involved. They are usually much less severe than in compressing lesions. Objective sensory impairment is deferred and less marked than the paralysis. The patient may have his attention first called to the presence of a weakness by fatigability on exertion or long walking or he may observe that the thighs seem weak in going up or down stairs. Should the segments involved be in the lumbar or cervical enlargements, atrophic palsy of the muscles supplied by the affected segments develops gradually. Disturbances of sphincter function are usually late in appearing.

Traumatic Myelitis.—Direct or indirect violence to the vertebral column may immediately impair spinal cord function. Injury without compression of the cord is often difficult to distinguish from the crushing lesions which result from severe contusions with fracture of the vertebræ. The immediate result of even mild forms of trauma may be edema so profound that it completely abolishes function at the level of injury, and constitutes what may be called a physiological block. The symptoms which result from simple concussion are practically the same as those due to contusion with diffuse petechial hemorrhages throughout the spinal marrow. Those referable to an injury at a given level are no different from the symptoms of the infectious and toxic type of myelitis except that root pains are frequent and prominent. Occasionally symptoms due to extension and even ascending degeneration appear long after apparent recovery.

Disseminated myelitis may be a sequel to any infection and is often due to syphilis. It is sometimes indistinguishable from acute multiple sclerosis. The scattered lesions produce appropriate symptoms from the beginning.

Diagnosis.—The anatomical diagnosis of well-established myelitis is simple. During the prodromal period of the acute form, paresthesiæ or root pains, weakness, or disturbances of sphincter function immediately arouse suspicion of myelitis. *Acute rheumatic fever* in its early stages may simulate myelitis. In the infectious form, preceding infectious disease is important. Both focal and local infections must be searched for. When a general infection is causal, the myelitis is apt to occur in the lumbar and cervical enlargements because of their abundant vascular supply. The spinal form of epidemic encephalitis and of epidemic poliomyelitis with involvement of the fiber tracts is discussed in other chapters.

The syndrome called *infective neuronitis* is probably a diffuse involvement of the spinal marrow in which the gray matter, especially of the anterior horns, is chiefly affected.

In toxic myelitis the onset is less abrupt. Search for underlying constitutional or predisposing environmental conditions is essential. Differential diagnosis between toxic and mild infectious myelitis is difficult because cultures of the spinal fluid are usually negative and recovery, which is the rule, precludes examination of tissues. Multiple neuritis may be difficult to distinguish. Differentiation between acute myelitis and *spinal thrombosis* or *hemorrhage* is often practically impossible. In elderly people with low blood-pressure and in cachectic patients, *thrombosis* should always be considered.

Difficulties may arise in establishing the etiology of the subacute or chronic forms. Syphilis is the usual cause. Naturally, chronic myelitis results from incompletely cured acute myelitis. *Kummell's disease*, in which there is productive arthritis following trauma to bones, may involve

the vertebral column and in a small per cent. of cases may compress the cord. The laboratory aids to diagnosis are helpful. A diagnosis of chronic myelitis implies the exclusion of *primary or metastatic tumors of the spinal cord and meninges, vertebral disease, combined sclerosis, multiple sclerosis, myelomalacia,* and *pachymeningitis with thrombosis or ischemia of the vessels of the cord.* Erosion from aneurysms is rare, but should be kept in mind.

Two generations ago hysteria and myelitis were at times difficult to distinguish. Now, with Workman's Compensation Laws everywhere, the differential diagnosis of hysteria and spinal cord injury is a common problem. Except to keep in mind that an hysterical patient may happen to have organic paralysis, nothing more need be said.

Examination of the spinal fluid is of especial importance. It is seldom that organisms can be cultured in the milder cases. An increase in globulin and cell-content is evidence of inflammation. In the majority of traumatic cases the fluid is discolored by pigment derived from blood, and flow of spinal fluid may be blocked by swelling of the cord. In subacute and chronic conditions when it is tinged with yellow, contains a marked excess of globulin, and few or no cells, there is a compressing lesion which has disturbed its flow. A positive Wassermann reaction, which is the rule in syphilitic myelitis, speaks for itself. When there is an increase in globulin, abnormalities of the colloidal gold curve must be interpreted with caution, especially when the Wassermann reaction is negative.

Complications and Prognosis.—Unless the upper cervical region of the cord is involved with ascent of the process to the medulla, death seldom results from the myelitis itself. Occasionally a case is seen in which the inflammation is so intense that abscess formation results with extension and wide-spread thrombosis. Such a condition is always fatal. The prognosis, while always serious from the standpoint of complete restoration of function, depends partly on the etiology and severity of symptoms and partly on the complications. The more complete the loss of spinal cord function, the less probable is complete recovery. The myelitis which complicates typhoid fever, influenza, and gonorrhea is serious. When associated with syphilis or the other acute infectious diseases it is not so apt to be fatal. The type due to dissemination or extension of a local or focal infection as a rule causes death. Cervical myelitis is always serious. In syphilitic myelitis prompt and intensive specific treatment usually evokes a favorable response.

The serious nature of myelitis often lies in its *complications.* Extensive decubitus is a forerunner of death, and in paralysis of the bladder an ascending infection of the kidneys is always imminent.

The rate of recovery varies considerably, and one may be agreeably deceived. As a general rule, when there has been a more or less complete block of function at a given level of the spinal cord, sensation attains its maximum improvement within three to six months and motor recovery is maximal within between six and twelve months. Complete return of sphincter function is the rule in mild cases. A spastic weakness of the lower extremities is the most prominent residual symptom. When the primary stage of inflammation or softening is chiefly exudative, recovery is more rapid and complete than when there has been productive inflammation with degeneration or hemorrhage which produces scar tissue.

In traumatic myelitis prognosis may be impossible during the first two

or three days because complete physiological block produced by edema is clinically identical with crushing of the cord. Examination of the spinal fluid at this time does not give definite data, and deformity of the vertebral axis does not conclusively prove that the cord has been crushed. According to Elsberg, indirect violence may cause a momentary dislocation of the lower cervical vertebræ with varying degrees of injury to the spinal cord. Improvement in traumatic myelitis may continue for an extended period of time. Adhesions between the meninges and the cord with, at times, local accumulations of spinal fluid may develop and be responsible for the delayed appearance of symptoms of compression. Gliomatous changes in the spinal medulla have been known to develop; they are associated with the syndrome of tumor of the spinal cord.

Treatment.—The treatment of myelitis includes, first, measures appropriate to the cause, and second, symptomatic remedies. Counterirritation and diathermy applied over the most involved segments of the spinal cord have been recommended on theoretical grounds, and if given carefully are not objectionable. There is no satisfactory local treatment, and the measures classed under the head of general nursing really comprise the entire therapy in acute or severe cases without a cause which can be specifically treated. Because of the susceptibility to decubitus, especially with lesions of the lumbosacral enlargement, it is wise to place the patient on an air bed. The body must be kept clean and dry. Frequent changes of position are helpful. Application of protective pads to the heels and sacrum is quite necessary. In the diet, plenty of "roughage" is desirable to prevent constipation. Colon irrigation every three days and daily oil enemas serve to keep the alimentary tract clean. Management of the bladder is perhaps the most important single item. When there is incontinence, some urine is usually retained. Urotropin may be given with acid sodium phosphate for a period and then replaced for a while with an alkaline diuretic in order to prevent cystitis. In patients with retention it is wise to avoid catheterization, for it is very difficult to avoid infecting the bladder directly by routine catheterization. Rupture of the bladder and hydronephrosis are equally rare. Cystitis is a serious and intractable complication which is particularly liable to be associated with lesions of the lumbar enlargement or conus when the trophic nerve supply is impaired. Manual expression at regular intervals, when performed skillfully, usually serves to relieve intense distress until either there is improvement or the bladder becomes automatic. A belladonna suppository or a hot enema may help start the flow of urine when there is retention.

A tent at the foot of the bed to keep the covers off the feet is useful. Slight elevation of the lower extremities aids return circulation and decreases edema. Very light massage and limited passive motion should be given to the paralyzed extremities after the first fortnight to aid in maintaining circulation and preventing contracture. No stimulating measures or electricity should be employed during the acute stages. Should a bedsore develop, dry dressings must be applied at first. If there is wide extension and necrosis, a wet dressing is preferable.

When the extremities are spastic, light massage and mild galvanism or diathermy may be given. Re-educative exercises are desirable for patients with persistent spasticity. For severe contracture, surgical measures including tenotomy, neurectomy, and muscle transplantation are to

be considered. Orthopedic appliances may enable the patient to walk. Electrotherapy finds its chief use in cases with persistent flaccid palsy.

In traumatic myelitis it is important to be certain that there is no deformity of the vertebral axis. Laminectomy should be performed without delay when the cord is compressed. This is almost always due to displaced vertebræ or fragments of bone; it is very rarely due to meningeal hemorrhage. It may, at times, be due to edema sufficient to cause not only physiological block, but mechanical compression of the cord. This is indicated by obstruction of the flow of spinal fluid. In the presence of such obstruction a laminectomy to enable simple decompression has recently been recommended.

George H. Hyslop.

SUBACUTE COMBINED SCLEROSIS OF THE SPINAL CORD

Subacute combined sclerosis of the spinal cord is a progressive condition of middle life, which is almost always fatal. It lasts from six months to four years, and is characterized by sensations of numbness and tingling of the hands and feet, and by increasing paralysis of the legs and hands. It results from degeneration in the posterior and lateral columns of the spinal cord. Anemia and *achylia gastrica* accompany the morbid process in the central nervous system.

Although twenty years ago this disease was thought rare, it is now comparatively common. This increase in incidence may be due in part to improved methods of diagnosis.

Etiology.—At one time the disease was believed to follow secondary anemia which had assumed pernicious characteristics, but it is now known that the symptoms produced by changes in the spinal cord often precede those of deterioration of the blood. *Free hydrochloric acid* may be absent from the gastric contents in the earliest stages of the disease, and this lack may, by permitting absorption of the toxic material from the gastro-intestinal tract, cause deterioration of the spinal cord and the elements of the blood.

The disease may first appear in the train of other exhausting disturbances, such as cancer or any prolonged illness, but just as often it develops without apparent cause. The writer has reason to suspect *chronic cholecystitis* as a potent etiological factor in the production of the chain of dilapidations which end in subacute combined sclerosis of the cord, with or without pronounced degeneration of the blood.

Incidence.—Combined spinal sclerosis is rare in individuals less than thirty-five years of age or more than sixty-five. The incidence is highest in patients between forty-five and fifty-five. The sexes are equally affected.

Morbid Anatomy.—Usually there are no lesions above the medulla, and the spinal cord remains macroscopically unchanged. Microscopically, extensive degeneration is evident,—chiefly in the mid-dorsal region, affecting the posterior tracts, the direct cerebellar tracts, and the direct and indirect pyramidal tracts. For the most part this is restricted to a discrete system.

Symptoms.—The patient may have had vague dyspepsia for some years before he gradually becomes aware of a sensation of deadness and "pins and needles" in the tips of the fingers of both hands and in the toes of both feet. These sensations are symmetrical and practically syn-

chronized in all four limbs. At first they are sharply limited to the extremities of the limbs; only in the advanced stages of the disease do they extend to the elbows or the knees.

No further symptoms may occur for some months even without treatment. Then, however, unsteadiness of gait, ataxia, especially in the dark, and poor stereognosis with consequent manual clumsiness may appear. Examination at this stage shows the cranial nerves to be normal. The pupils are never of the Argyll-Robinson type, as the condition is not produced by syphilis. There may be sensory ataxia in the arms as in tabes. Astereognosis, dependent on impairment of the sense of position in the fingers, is often accompanied by a lowering of vibration sense as well. The abdominal reflexes are depressed or absent. The knee-jerks are probably still active. Absence of ankle-jerks and a bilateral Babinski phenomenon are signs of degeneration of the posterior column and the motor column, respectively. Sensory losses in the lower, as in the upper limbs, produce ataxia and a positive *Romberg sign.*. The sphincters at this stage are rarely affected.

In most instances the disease is progressive. Girdle pains are felt as tightness and pressure rather than as shooting pains, as in tabes. Acute abdominal distention in attacks of several days' duration, bladder and rectal retention and incontinence, and increasing weakness and ataxia of the legs and arms within a year render the patient bed-ridden. The knee-jerks will then probably have disappeared, and increased losses of posterior column sensation will be found in the legs and hands; but a double exterior response can usually be elicited until death. Progressive prostration accompanies these local disabilities and if, as is usual, there be continuous blood decline, the deterioration of general function is thereby accelerated. Mental disturbance, bedsores, and total palsy of limbs and sphincters constitute the symptoms of the last stages. Death is produced by heart failure or intercurrent pulmonary infection.

Diagnosis.—The following outline may be useful in solving the difficulties which often arise in distinguishing subacute combined sclerosis of the cord from disseminated sclerosis, multiple neuritis, and tabes dorsalis:

Subacute Combined Sclerosis of the Cord.	*Disseminated Sclerosis.*
Incidence highest between forty-five and sixty.	Incidence highest between twenty and thirty-five years of age.
Progressive course.	Remittent episodic course.
No ocular symptoms.	Transient blindness or blurring of vision. Transient double vision.
No change in the optic nerve.	Pallor of the temporal portion of the optic disks.
Sphincter trouble in late stages.	Sphincter trouble in early stages.
Deep reflexes usually absent.	Deep reflexes rarely absent.
Subacute Combined Sclerosis of the Cord.	*Multiple Neuritis.*
No definitely known cause.	Cause may be alcohol, lead, arsenic, encephalitis.
No muscular tenderness.	Muscular tenderness.
Loss of posterior column sensation; loss of the senses of position, vibration, and deep pain.	Loss of peripheral sensation; loss of superficial sensation of "glove and stocking" type.
Abdominal reflexes absent. Double extensor plantar reflexes.	Abdominal reflexes present, and extensor plantar reflexes absent.
Sphincter palsy in late stages.	No sphincter involvement.
Motor palsies referable to cord.	Peripheral motor palsies (dropped wrists and feet).

Subacute Combined Sclerosis of the Cord.	*Tabes.*
No history of syphilis. Tests for syphilis negative.	Positive history of syphilis. Syphilitic tests positive.
Cerebrospinal fluid normal.	Lymphocytosis in spinal fluid. Wassermann test positive.
Pupils normal.	Pupils fixed or sluggish in response to light.
Great loss of motor power.	Slight loss of motor power.
Extensor plantar reflexes.	Flexor plantar reflexes.
Rare lightning pains.	Common lightning pains.

In any of these symptom-complexes the presence of achylia gastrica or deterioration of the blood, or both, enormously increase the probability that the concomitant nervous symptoms are manifestations of subacute combined sclerosis of the cord.

Treatment.—Search should be made for areas of infection or toxemia. The teeth should be examined, and also the tonsils and sinuses. The malign influence of a sepsis of the gall-bladder in initiating the process which ends in pernicious anemia or subacute combined sclerosis of the spinal cord has already been mentioned.

Dilute hydrochloric acid in maximal doses (1 or 2 drams in a glass of water with meals) should be given early and continuously. Arsenic, iron, and red bone marrow are useful. Blood transfusion must not be delayed; it should take place shortly after the anemia has appeared, and should be repeated regularly and often.

FOSTER KENNEDY.

MULTIPLE SCLEROSIS

(*Insular Sclerosis, Sclérose en Plaques, Disseminated Sclerosis*)

Definition.—Multiple sclerosis is a diffuse, disseminated, structural disease essentially of the central nervous system, characterized by a degeneration in multiple areas, which leads to widely diversified symptoms, often of transient character, involving chiefly the motor system.

History.—The first recognition of the disease is credited to Cruveilhier (1835), although it was Valentiner (1856), who first tentatively described the symptomatology. Charcot and Bouchard (1862–63) clarified the conception of the syndrome and established the triad of signs—nystagmus, scanning speech, and intention tremor—as pathognomonic of the disease. Since the important monograph by Bourneville and Guerard appeared in 1869 the literature on the subject has become voluminous, through investigations in Germany, Scotland, and later in the United States.

Incidence.—The disease occurs most frequently in young adults; its onset is rare in patients less than fifteen and more than forty-five years of age. Evidence thus far obtained points to its greater prevalence in Europe than in America, a fact which may well be due to less accurate diagnosis in this country. Multiple sclerosis is one of the commonest organic diseases of the nervous system, and by some observers has been regarded as even more prevalent than syphilis. Further statistics should be obtained.

Etiology.—The cause of the disease is still in doubt. Infections, thermal influences, traumatism, intoxications by lead, arsenic, and the like, and very recently a specific spirochete, not as yet generally recognized, have been regarded as possible etiological factors.

Morbid Anatomy.—The macroscopic changes are widely distributed throughout the central nervous system, irrespective of gray or white matter, and the special neurone tracts. They appear as areas of degeneration of varying size, frequently sharply circumscribed without immediate relation to blood-vessels. Microscopical examination invariably reveals a primary change (tumefaction) of the myelin sheaths, followed much later by a certain degree of axone destruction. This early myelin degeneration constitutes the sclerotic patch characteristic of the disease. Changes in the neuroglia are secondary. The reason for the disparity often observed between the apparently destructive pathological lesions and the symptoms is the persistent preservation of the conducting axones, in spite of extreme myelin degeneration. The characteristic tendency to remissions is explained by the restoration of axone function in affected areas, through which in the acute stage no conduction was possible. The roots of the spinal nerves may undergo change similar to that in the brain and cord.

Symptoms.—As would be expected from the pathological changes, the syndrome of multiple sclerosis is more varied than that of any other single organic disease of the nervous system. The three classical symptoms, nystagmus, scanning speech, and intention tremor, appear very inconstantly and are by no means essential to diagnosis. Because of the multiplicity of the lesions and the varying sequence of their appearance in different parts of the cerebrospinal axis, the resulting signs and symptoms must be irregular in character and development. Spastic conditions in general predominate; muscular atrophy is rare; sensory disturbances are definitely subordinate to motor defects; and pain seldom occurs. A recent tabulation gives the following signs in order of diagnostic importance: fatigue, increase of deep reflexes, nystagmus, ataxic tremor of upper extremities and head, loss of abdominal reflexes, disordered gait and station, disturbances of speech (often scanning), pallor of the optic discs on the temporal sides, uncontrolled emotionalism, remissions, transitory palsies of ocular nerves, vague sensory disorders, vesical difficulty, mental changes, and others of less frequent occurrence. Much stress should be placed on the frequent development of spastic conditions at some stage of the disease, and less upon the supposedly characteristic tremor and scanning speech. The signs and symptoms naturally depend upon the localization of the lesions and are as varied as the localization. Consequently, spastic conditions are more likely to occur on account of the length of the motor (pyramidal) tracts than are nystagmus, scanning speech, or tremor, which have a much more limited localization. A tendency to remissions is a second most important symptomatic peculiarity.

Diagnosis of so-called typical cases presents no difficulties. In no other condition do the speech defect, the tremor on intended movement, and nystagmus, co-exist in the same degree, but this very fact has led to much confusion. Experience has shown that the so-called *Charcot triad* is so inconstant that it should not serve as a diagnostic criterion. When present, its evidence is conclusive; when absent, as in a large proportion of cases, other groupings of signs and symptoms should be considered, *i. e.*, spasticity, loss of abdominal reflexes, transient palsies in various nerve distributions, tremors and atypical speech defects, emotional instability, and an irregular course, with a strong tendency toward mental deterioration. That such a disorder, with its recognized pathological basis, may

simulate various functional and organic diseases, is evident. If this fact be borne in mind, mistakes in diagnosis should be less frequent. Examination of the spinal fluid affords some help in that a paretic gold-sol curve is very frequently demonstrable (50 per cent. of Ayer's series), as well as certain minor changes in the cellular content and other constituents. A consistently negative Wassermann reaction in blood and spinal fluid differentiates the disease from the various forms of syphilis, with which in its purely clinical aspects it is often confused.

Prognosis.—Multiple sclerosis is finally fatal or leads to fatal complications. Its duration is variable and may be several decades. The strong tendency to remissions may simulate recovery, but evidence that recovery has actually taken place in any unquestioned case is still lacking.

Treatment.—Since the cause of the disease is as yet undetermined, there is no specific or really efficient treatment. The possibility that a spirochete may be the cause is still too vague a basis for systematic treatment, although arsenical preparations, including sodium cacodylate and mercury, have been given with some evidence of benefit. Recently, patients have been treated with malaria, and with typhoid vaccine in addition to malaria, but without beneficial results, although some were temporarily improved. Staphylococcus vaccine gave less satisfactory results than the combination of malaria and typhoid, and malaria alone was the least satisfactory. In general, the usual drugs and mechanical measures must be employed to combat the various manifestations as they arise.

E. W. Taylor.

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DIFFUSE AND FOCAL DISEASES OF THE SPINAL CORD

AFFECTIONS OF THE BLOOD-VESSELS OF THE SPINAL CORD

Branches of the anterior spinal artery enter the central part of the cord through the ventral fissure and supply all the gray matter except a large part of the posterior horn. Vessels also penetrate from the periphery into the white matter of the posterior column. Although the white and the

gray matter are not supplied by two independent systems, there are regions of the cord in which the gray matter receives its supply exclusively from the central arteries, and the peripheral white matter obtains nourishment only from the vasocorona. The veins of the spinal cord are arranged like the arteries, except that they are much more in evidence on the surface of the cord.

Anemia.—The rapid development of paralysis after profound hemorrhage may perhaps be explained by resulting anemia of the spinal cord. In pernicious anemia, probably both the lesions in the blood and those in the cord are produced by some common hypothetical toxin.

Endarteritis and Arteriosclerosis.—Endarteritis of the cord is part of a general process associated with lues or senile atheroma. Foster Kennedy and Elsberg have observed sclerotic changes in the vessels of the cord in individuals with neuritis of the cauda equina.

Arteriosclerosis of the cord is of several types: that characterized by senile degeneration of the posterior columns and evidences of posterior sclerosis (diminution of the deep reflexes and disturbances in joint mobility and vibratory sense); that which involves the lateral columns and produces spastic paraplegia without sensory changes or cystic symptoms; and that evidenced by softening of the cord (myelomalacia) with irregular lesions in both the white and gray matter, and with symptoms of disease of the anterior horn-cells (isolated atrophy with electrical change in the muscles involved). In the author's experience the first type has never been associated with the clinical manifestations of posterolateral sclerosis (anemia, achlorhydria). The mechanism, however, is probably the same as that of progressive funicular myelopathy.

Spinal thrombosis may produce the Brown-Séquard syndrome, and syringomyelic disturbances are said to occur in pachymeningitis luetica after blocking of the lumen of the spinal vessels by organized exudate.

Meningeal hemorrhage may be epidural, intradural, or subdural; the epidural type is usually the result of trauma which ruptures the venous plexuses; intradural bleeding less frequently follows trauma. Both epidural and intradural hemorrhage are relatively unimportant because they are merely phenomena of a more severe injury. Subdural hemorrhage follows trauma of the nervous system, and is also frequently associated with obstetrical injury, convulsions, fever, and hemorrhagic diathesis. It is much more common than the extradural type. It rarely compresses the cord. The most frequent cause of subarachnoid bleeding is rupture of an aneurysm at the base of the brain. In some cases of apoplexy, however, the blood may find its way through the fourth ventricle of the brain into the subarachnoid space.

Symptoms.—In some instances meningeal hemorrhage produces no symptoms, but, as a rule, the onset is marked by sharp pain in the back and symptoms referable to the nerve roots. There may be muscular spasms or paralysis of the arms or legs. Except when an aneurysm ruptures at the base of the brain there are no cerebral signs. The type of cord symptoms depends on the level of the lesion.

Prognosis.—The prognosis varies with the cause. Recovery may follow hemorrhage associated with constitutional disease.

Treatment.—Since the cord is rarely compressed removal of blood-clots from the spinal cord by operation does not often give relief.

Hematomyelia (*Apoplexy of the Cord*).—In comparison with apoplexy of the brain that of the cord is rare. It occurs most often in individuals between twenty and forty years of age, and is much more frequent in men than in women. It may be a complication of syringomyelia.

Etiology.—Spinal bleeding is apparently not due to the same cause as cerebral bleeding, although the sclerotic changes associated with the latter are not uncommon in the spinal arteries. The most important cause is *trauma*. Even when the spinal column itself does not appear to be injured hemorrhage may ensue. A fall on the buttocks or legs, direct injury to the spine, sudden forward flexion of the head, or a headlong dive may produce hematomyelia. The lifting of a heavy load and military drill are also known to be precipitating factors. Inflammatory and neoplastic lesions also serve as predisposing conditions. Spinal hemorrhage is favored by an underlying diathesis. Arteriosclerosis seldom causes bleeding into the cord or its membranes. Difficult labor is a cause of hemorrhage in the newborn.

Morbid Anatomy.—Although hemorrhage may occur at any level, it is most often found in the cervical enlargement. Bleeding may extend throughout the gray matter, or be restricted to one side of the cord and spread vertically. Frequently even when there are no apparent abnormalities on the surface of the cord, palpation with the finger may reveal swelling. The color of the cord may be bluish-red because the blood-clot shines through the surrounding white matter. The extravasation is in some cases limited to one or two segments, in others it extends through many levels, and frequently it assumes a spindle-like shape. Since the gray matter contains more blood-vessels than the white and is a looser tissue, the white matter is seldom involved except at the site of maximum hemorrhage. The lateral columns are usually spared. When of very long standing, the pathway of the hemorrhage is represented by a cyst containing clear fluid.

Microscopical examination of the cord lesions reveals edema and necrosis. After a few days evidence of glial proliferation can be found and granular cells abound; later, only local sclerosis remains. If the anterior horn-cells are destroyed, atrophy of the ventral fibers is apt to ensue.

Symptoms.—The symptoms usually begin suddenly and suggest a transverse lesion of the cord. The patient falls to the ground as the result of weakness in the legs, and exhibits sensory changes and disturbances in control of the sphincters. Trophic phenomena soon appear. At times the symptoms are less fulminating, and the complete syndrome does not develop until secondary necrosis and inflammation have taken place. At the onset there may be pain in the back and stiffness. In mild cases symptoms are sometimes lacking or so slight as to suggest a functional disorder. When this occurs only very careful search reveals the isolated muscular atrophy (with electrical changes), the slight but characteristic sensory disturbances, and the fibrillation.

Many symptoms depend on the location of the hemorrhage. If it is in the lumbar region, there is flaccid paralysis of the lower extremities with loss of deep reflexes, sensory changes which involve pain and temperature for the most part (dissociated type), and atrophy of the muscles. When the cervical enlargement is the site of the lesion as it often is, atrophic paralysis of the upper extremities and spastic paralysis of the lower limbs (spinal hemiplegia) result. Involvement of the lower cervical cord may cause

sympathetic phenomena (reduction of the pupils, pseudoptosis, and enophthalmos). Taylor and Collier describe papillo-edema with hemorrhage of the upper cervical cord, and the author has observed choked disks with this lesion. The hemorrhage may extend upward to the medulla and even into the pons. Very frequently an acute Brown-Séquard syndrome develops with symptoms of partial atrophic paralysis of the arm, spastic paralysis of the corresponding leg, and contralateral disturbances in the pain and temperature senses. At times the symptom-complex is that of a transverse myelitis. The writer has observed bladder and rectal symptoms and a typical "riding-pants" anesthesia with bleeding into the conus. Patients who survive improve markedly within a few weeks. The paraplegia diminishes, the bladder may recover its function, and only those symptoms which are due to permanent damage to the cord (degenerative atrophies and the dissociated sensory disturbances) remain.

Diagnosis.—Hematomyelia must be differentiated from *meningeal hemorrhage* which is characterized by pronounced root phenomena, pain in the back, and stiffness and tenderness of the muscles. In epidural extravasation there is little pain. Lumbar puncture may permit differentiation between epidural and subarachnoid bleeding. Hemorrhage in the spinal cord must also be distinguished from *acute myelitis*. This is usually less sudden in onset, is associated with fever, and runs a more protracted course. *Thrombotic softening* of the cord caused by obliterating vascular disease may be recognized by the usual luetic history, positive serological data (blood), and by the evidences of definite spinal "level" involvement. *Acute poliomyelitis* is, of course, not associated with sensory changes.

Prognosis.—Except when there is a severe transverse lesion or extension of the process to the medulla the patient usually improves. Complete recovery, however, is rare. Invasion of the phrenic area renders prognosis poor.

Treatment.—In the treatment of hematomyelia, absolute rest for two or three weeks is essential. The patient should assume the lateral prone posture and avoid coughing and straining at stool. Care must be taken to prevent decubitus and bladder infection. Later, warm baths and electrical therapy are desirable. Epidural hemorrhage may be treated surgically.

E. D. Friedman.

TUMORS OF THE SPINAL CORD AND RELATED STRUCTURES

(*Vertebral Tumors, Meningeal Tumors, Tumors of the Cauda Equina*)

The most common tumors of the cord are glioma and gliosarcoma and of the cord membranes fibroma, and meningioma. The term "meningioma" includes the psammoma and the histologically discutable endothelioma or arachnoid fibroblastoma of Mallory. Rarer forms are lipoma, angioma, cysts including the echinococcus cyst, syphiloma, and tuberculoma. Among primary vertebral tumors are sarcoma, osteoma, and chondroma. Of the metastatic vertebral tumors carcinoma is the most frequent. Tumors are classed as intramedullary when they involve the cord substance proper,

and extramedullary when they lie outside of it. Extramedullary tumors may be intradural or extradural.

Symptoms.—The following symptomatology is typical of an extramedullary intradural tumor in the mid-dorsal region. Superficial spinal root pain of varying intensity and duration which radiates in a girdle sensation, unilaterally at first and later bilaterally, is the first symptom. This results from the gradual compression of the cord and its sensory roots at a definite level. After a variable length of time during which the patient is often thought to have an abdominal ailment, signs of early spastic paraplegia appear, with subjective stiffness in the legs, increase of the lower tendon reflexes, and signs of involvement of the pyramidal tract, such as extension of the great toe on plantar stimulation (Babinski's sign). About this period sensory disturbances are manifested by a diminished perception of pain and temperature below a certain segmental level. This is an important guide to the location of the tumor. This change is recognized only by careful search, for sensation is still differentiated below the lesion. In the final stage of marked cord compression there is severe spastic paraplegia, anesthesia below the level of the lesion, automatic cord reflexes such as involuntary drawing up of the legs, and loss of anal and rectal sphincter control. If not guarded against particularly, bed-sores and bladder infection may complicate the syndrome.

Diagnosis.—Compression of the spinal cord blocks the subarachnoid space and the circulation of cerebrospinal fluid, and changes occur in the fluid which are of considerable diagnostic importance. Froin described a fluid of canary yellow color, rich in protein, which clots rapidly, to which he gave the name "*xanthochromia.*" In cases of early compression Nonne found an increase in the protein content without change in color, clotting time, or cell content. Ayer, of Boston, has advocated combined puncture of the cisterna magna with that of the lumbar sac in order to study the respective pressures and the flow of fluid in cases of suspected block. In ordinary lumbar puncture while the needle is *in situ*, jugular compression (Queckenstedt), by varying the subarachnoid fluid pressure, gives evidence of the presence or absence of a block.

The Roentgen rays have been of service in the diagnosis of cord tumor directly and also indirectly by outlining substances which have been injected into the subarachnoid space of a density different from that of the spinal tissues. Both air and lipoidal have been thus used. Sicard injects lipoidal (iodized oil) above the supposed site of the tumor. It then descends to the level of the tumor where it is sharply outlined by the Roentgen ray. If there is a communication below, the oil drains into the lumbar sac.

Tumors anterior to the dentate ligament which do not involve the posterior spinal roots may produce no pain and thus cloud the diagnosis. The relation of the tumor to the anterior spinal roots or anterior horn-cells determines the amount of atrophy and flaccid paralysis at the compression level. From the diagnostic standpoint the atrophies, according to Collier, are often quite as important as the upper limit of sensory change in determining the compression level. The upper limit of elicitation of the pyramidal automatic cord reflexes (Babinski) may demonstrate the lower level of the compression. Because of the obliquity of the spinal roots an extramedullary tumor may involve these roots and the cord fiber systems at relatively different segmental levels, and cause atrophy above the pyramidal

lesions. In intramedullary lesions the reverse may be true. The Brown-Séquard syndrome, at least incomplete, is produced by extramedullary as well as intramedullary tumors. In certain cases there are no absolute diagnostic criteria by which intramedullary and extramedullary tumors may be differentiated. Tumors in certain parts of the spinal axis have distinguishing features; cervical tumors characteristically produce quadriplegia and involve the ciliospinal center and the phrenic nerve. Vertebral carcinoma is one of the most painful affections known, and before the *x*-ray evidence or other manifestations of the disease can be found, the patient may be thought hysterical because of loss of emotional control produced by pain. Tumors of the conus evoke a characteristic riding-breeches anesthesia, early loss of sphincter control and symmetrical peroneal palsy, and foot-drop by direct involvement of the sacral centers. Caudal tumors are characterized by severe bilateral sciatica-like pain. This is best relieved by sitting or lying in bed with the lower limbs in extreme flexion in order to relieve root tension.

Any paraplegia of gradual onset without evident cause may be suspected of being due to a cord tumor. *Subacute toxic degeneration* of the cord may be difficult to differentiate in the early stages if the usual anemia is absent. The paresthesias, absence of definite pain, and marked disturbance of deep sensation, with preservation of superficial sensation, are important differential guides. *Erb's syphilitic spastic paraplegia* usually has a definite syphilitic history and positive serology. *Syphilitic meningomyelitis* may be confusing, although the biological aspects of the fluid are often deciding factors. *Multiple sclerosis*, although characterized by a spastic paraplegia, has usually other cardinal symptoms. *Amyotrophic lateral sclerosis* and *primary lateral sclerosis* are pure motor syndromes. *Tuberculosis* of the spine is frequently evidenced by deformity or *x*-ray shadows. *Gumma* is exceedingly rare. *Hypertrophic cervical pachymeningitis* may closely simulate an extramedullary growth and forms in effect a tubular new growth with marked root pain and atrophy in the cervical region. *Circumscribed serous meningitis* with adhesions of the arachnoid may cause cyst-like formations which compress the cord. An *inflammatory disease of the cauda*, described by Kennedy and Elsberg, may be impossible to differentiate from tumors in clinical and serological aspects. *Tumors high in the cervical region* which implicate the foramen magnum may simulate brain tumor in that they cause choking of the disks, bulbar symptoms, and occipital headache, due to pressure on the highest cervical roots. It is evident from the foregoing that cord compression may be simulated by many different disorders. Because of the physiological suppliance and overlapping of the sensory spinal distribution to the skin, the anesthetic level on the body surface may be lower than the corresponding root area of compression and the tumor may be sought for too low. It is customary, therefore, to add at least one spinal segment above the anesthetic segment in determining the compression level. It must be remembered that the vertebral bodies and spines, and the cord segments, have a different numerical relationship, and suitable charts or tables must be consulted to ascertain the spinal level after the involved cord segment has been located.

Treatment.—Brilliant results have often followed the surgical removal of extramedullary cord tumors. Patients with marked paraplegia accompanied by sensory changes and sphincter involvement have been almost

completely restored to normal. When necessary the removal of as many as five spines and laminæ seems not to interfere with later function of the vertebral column. It is a wise precaution to keep the patient prone after operation if there is any danger of decubital gangrene. Deep *x*-ray therapy may also be used, particularly in the inoperable cases, in tumors of the cervical region when the operative risk is relatively great, and for patients who refuse operation.

SYRINGOMYELIA

Syringomyelia, or the formation of cavities in the cord, may be due to the breaking down of a central glioma of the cord which originates in the subependymal glia. For this reason it is often described with cord tumors. Typically the condition may persist for many years and produce the characteristic loss of temperature and pain sense, while tactile sensation is retained. The physiological explanation may be found in the involvement of the crossed pain and temperature fibers in the anterior commissure, and the sparing of tactile fibers in the posterior columns. Painless burns which become infected may be the first complaint which brings the patient to a physician. Involvement of the motor cells of the anterior horns may produce marked atrophies as of the small hand muscles, and involvement of the pyramidal tract may produce a definite spastic paraplegia. Trophic and atrophic changes are frequent. Unusual forms of syringomyelia have been described as *analgesic panaris* (Morvan's disease), and as *syringobulbia*. The vertebral column may be markedly scoliosed and the thorax deformed (*thorax en bateau*). Other conditions than gliosis may cause the formation of cavities in the spinal cord, for instance, hematomyelia, pressure, and vascular disease. The history of the case, the character of the onset, and the symptomatology should aid differentiation.

The *treatment* of syringomyelia should be such as to arrest the process. Deep *x*-ray therapy should be tried. A number of patients have been reported to be benefited and relieved from pain after its use.

Walter F. Schaller.

Diffuse and Focal Diseases of the Brain

APHASIA

Definition.—Aphasia, as ordinarily understood, is a disorder of language of either the emissive or receptive type, which is produced by a lesion in certain regions of the cerebral cortex or subcortical nerve-fibers, usually on the left side of the brain.

History.—Gall, about 1800, was the first to suggest that the brain was made up of organs which controlled the "vital and moral faculties of man." Gall was not a quack and not the phrenologist he is usually described to be, but a scientific pioneer in brain physiology, and his work had a great influence on the thought of his time. He believed that speech and the memory for words were situated in the frontal lobes.

About 1861 Broca began to give us our first important knowledge of speech defects due to lesions of the left hemisphere. His ideas were based on certain cases of aphasia in which the brain was examined after death. Lesions were found in the posterior part of the second and third frontal convolutions, as well as elsewhere in the brain. Broca described some of these speech defects as "aphémie," although he divided cases into two groups—"aphémie" and "amnésie verbale." The aphemic patient is able to understand what is said to him and can recognize words, although he cannot pronounce or repeat them. His vocabulary is reduced so that he can say nothing at all, or perhaps only a few short words or oaths. The amnesic patient can speak and pronounce words correctly, but they may have no meaning at all. Broca believed that "aphemia" was produced by a lesion in the third frontal convolution of the left side.

The left inferior frontal gyrus of the brain is known as Broca's convolution. Broca's area lies within Broca's convolution, embracing the base of the inferior frontal gyrus. It extends, perhaps, also to the adjacent part of the lowest region of the precentral convolution and to the anterior part of the insula.

Trousseau supported Broca's views in the discussion which followed Broca's papers and introduced the word "aphasia" to replace Broca's "aphemia."

Hughlings Jackson in 1864 began to write about the subject in quite a new way, attempting to tell us more particularly the nature of aphasia. He pointed out that aphasia on the emissive side is the inability to form or express a proposition in words, and, on the receptive side, it is a failure of the mental processes which underlie perceptual recognition of a proposition—the more abstract the proposition, the harder it is for an aphasic to formulate it, or, on the other hand, to understand it. The work of Jackson was of great importance in many other ways and is only now receiving its full measure of appreciation.

Bastian (1869) and Baginsky (1871) began to introduce schemas and diagrams of the speech centers and their relations to one another by nerve pathways, attempting to reduce the knowledge of the subject to mathematical exactness and to postulate many theoretical types of aphasia. Bastian described word deafness.

Wernicke in 1874 localized the center for auditory images in the first left temporal convolution. He believed that oral speech alone possessed cortical centers, one was guiding and the other emissive. Between these two lay the island of Reil, and therefore there were three possible kinds of aphasia. The first was sensory with the lesion in the temporal lobe; the second was motor with the lesion in the third frontal convolution; and the third was a conduction aphasia with the lesion between these two centers.

"Wernicke's Zone" is the region including the posterior half of the first two temporal convolutions, the angular gyrus, the supramarginal gyrus, and their subcortical areas.

In 1906 Marie, one of Broca's interns, contributed a new theory to the discussion on aphasia. His view, in brief, was that there was only one kind of aphasia, the aphasia of Wernicke, and that the motor aphasia of Broca is a combination of Wernicke's (sensory) aphasia with "anarthria." Anarthria he ascribed to a lesion of his "lenticular zone," which is a quadrilateral defined anteriorly by a vertical plane passing through the anterior marginal fissure of the insula and posteriorly by a parallel plane through the posterior marginal fissure of the insula; within, it is bounded by the lateral ventricle, and without by the surface of the insula. Above, it extends to the suprajacent convolutions, below to the subthalamic region. The third frontal convolution and its subjacent white matter is excluded.

Moutier, in 1908, published an important monograph on aphasia from Marie's laboratory. Déjerine took issue with Marie's view, and especially insisted that the term "anarthria" should be used only for troubles of articulation (as in pseudobulbar palsy, etc.).

Head, in 1910, began to devise new tests for aphasia as a result of his belief in Jackson's views of the subject. He regrouped cases of aphasia as follows:

1. Verbal aphasia: Defective word formation, both in internal and external speech.
2. Syntactical aphasia: Want of coherence and a tendency to talk jargon.
3. Nominal aphasia: Defective use of nouns, both spoken and written.
4. Semantic aphasia: Deficient comprehension of the full significance of words and phrases.

Head introduced the term "symbolic thinking and expression." Head's contribution to the subject in his papers of 1920 and 1923 in "Brain" was mostly in the nature of an analysis of what aphasia is from a psychological point of view. He described his cases as showing certain defects in what he called symbolic thinking and expression, and pointed out that defects in these two spheres included not only imperfections in spoken and written language and in the understanding of them, but also such things as the inability to recognize the difference in symbolic meaning of the big and the little hands of a clock; the inability to recognize the difference between making a turn to the right and to the left, etc.

Types of Aphasia.—Because the condition has not been fully understood and because various terminologies have been employed by different investigators, it may be well to define briefly a few of the terms commonly encoun-

tered. "*Cortical motor aphasia*" is the name sometimes given to a speech defect produced by a lesion in Broca's convolution. "*Subcortical motor aphasia*," "*pure motor aphasia*," and the "*pure word-dumbness of Déjerine*" are terms used to describe a condition supposedly produced by interruption of nerve-fibers which connect Broca's area to the center for articulation in the foot of the central convolution. To the condition in which spontaneous speech is lost and the ability to repeat words is retained the name "*transcortical motor aphasia*" (Lichtheim's) is given. This disturbance is caused by a cerebral lesion outside Broca's area, which interrupts the fibers passing to Broca's area from regions where word memories are aroused. *Cortical sensory aphasia* is the disorder caused by abnormality in the cortex of the temporal lobe. The terms "*subcortical sensory aphasia*," "*Wernicke's pure word-deafness*," and "*Déjerine's pure sensory aphasia*" are all used to describe functional separation of the sensory speech center from the auditory receptors by a lesion in the subcortical nerve-fibers. Interruption of the

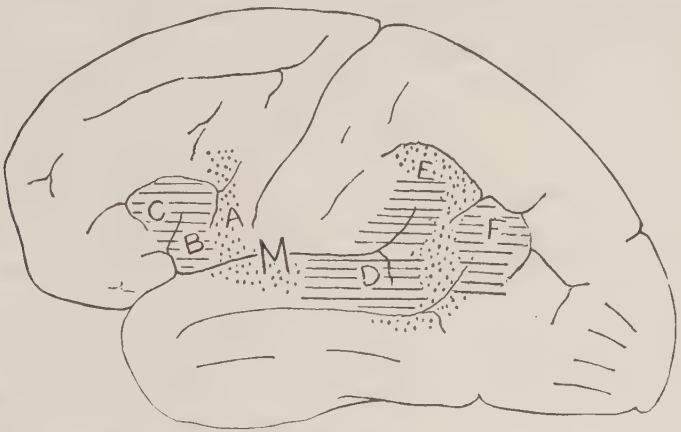

Fig. 28.—The zone of language and the localization of the main types of aphasia: A, B, C, Motor aphasia, characterized by aphemia. D, Temporal lobe aphasia, characterized by word-deafness, anomia, jargon. E, Supramarginal gyrus aphasia, characterized by global aphasia and apraxia. F, Angular gyrus aphasia, characterized by alexia. M, Mixed aphasia, the common type of aphasia, characterized by aphemia, agraphia, some alexia with word-deafness, and marked hemiplegia.

fibers which connect Wernicke's zone with Broca's area (in the Island of Reil for example) is known as *conduction aphasia*. This does not destroy voluntary speech, but produces paraphasia, *i. e.*, skipping of words, frequent repetition, and confusion. "*Dyslexia*" is the name applied to a condition in which the patient can only read a few words or sentences before he becomes fatigued and refuses to continue. "*Echolalia*" signifies involuntary repetition of the last words spoken to the patient. Since a full description of all these types is impossible here, the following discussion will include only motor and sensory aphasia.

Motor aphasia is a condition in which a lesion in the speech center destroys the power to utter words which are in the patient's mind. Its association with difficulty in reading depends on the previous mental habits of the individual. For instance, the tendency to pronounce distinctly but silently each word that is read would doubtless lead to complete

loss of the ability to read as well as to speak if a lesion developed in Broca's area. Other variations in the clinical evidences of such lesions are probably to be explained by other mental habits. Some individuals can normally remember words or figures only after seeing them, while in others retention is possible after they have been merely heard. The great personal variation in the ability to form abstract propositions is sufficient to account for the various degrees of diminution in this power associated with lesions of similar situation and extent. Because the few words which an aphasic patient can use are expletives and parts of the native language which have become automatic, it has been suggested that the right hemisphere is responsible for their control. It is quite common for a patient to be able to use a few words of profanity, such as "Damn," "Oh Hell," etc., and it is well known that anyone who has acquired some facility in the use of a foreign language late in life may lose this entirely after becoming aphasic although he is still able to speak his native language. The ability to solve simple arithmetical problems may be more or less affected (akalkulia).

In determining the location of the causative cerebral lesion it is first necessary, as Kennedy has pointed out, to determine on which side of the brain the speech centers lie. To do this it is essential to know whether the patient and also his stock are habitually right- or left-handed, for heredity rather than use seems to determine whether the speech centers are on the right or left side of the brain. The fact that the ability to write is often lost in aphasia is probably to be accounted for by involvement of the posterior end of the second frontal convolution by the lesion.

Perhaps the clearest conception of motor aphasia can be given by citing a typical case:

Sir James Purves-Stewart in discussing Head's work described a condition in which all speech was suddenly lost, although the intelligence remained unimpaired. There was facial weakness on the right side. The patient was able to understand and execute all sorts of verbal commands, such as bending the thumb half-way or straightening it out. The Babinski reaction was found on the right side. No paralysis of arm or leg was discovered. At autopsy there was a small lesion in the lower third of the left precentral gyrus due to embolic blocking of a small cortical arteriole. This extended deeply into the operculum, but affected neither the insula nor the basal ganglia. Marie's "lenticular zone" was not involved. There was no other lesion elsewhere in the brain.

A somewhat atypical case mentioned by Bailey may also be of interest:

A slight difficulty in reading was followed by inability to write a letter, and later by definite aphasia, mainly of the motor type. The patient had great difficulty in pronouncing words, although she knew what she wanted to say. Her comprehension of written speech was perfect, and she could execute verbal and written commands easily. The difficulty in reading and writing persisted, although she could write her name. There was some numbness in the right hand, and Jacksonian fits involving the right face and tongue were associated with some residual weakness of the right lower side of the face, and right hemihypesthesia with equivocal Babinski on the right side. In this case the difficulty in reading was probably due to inability to say or write the words and not to inability to comprehend the meaning of the words—not a true alexia.

A nodule of metastatic melanosarcoma (3 x 2 cm.) was removed from the foot of the left second convolution at operation.

Sensory aphasia is the term usually applied to inability to understand spoken or written language (word-deafness, word-blindness, alexia).

Word-deafness is caused by a lesion of the posterior part of the left superior temporal convolution. It is evidenced by inability to understand words which are heard, by inability to repeat words, and sometimes, although not as a rule, by loss of power to speak anything except jargon. The

patient is usually unaware of his errors of speech and is, therefore, not distressed by them as is the patient with motor aphasia. Word-deafness seems to be associated with some degree of mental impairment, which may in certain instances arouse suspicion of insanity. When the word-deafness is not absolute the patient may understand an expected sentence from the doctor, such as "put out your tongue," while he cannot carry out other spoken commands. Gowers points out that expectancy seems to lower the resistance in certain nerve combinations, just as it does so often in sleep. Patients frequently have great difficulty in voluntarily naming an object which is held in front of them, even when their normal vocabulary is large. This so-called *anomia* is not associated with loss of appreciation of the use of an object. Sometimes a patient who cannot recollect a name after visual perception alone is able to do so when a second sense such as that of touch is called into play. Another type of this indirect method of recollecting words is well illustrated by the author's experience. On being asked what his telephone number was one patient said "Olive, 2-34-56-789." The number was "Olive 2469" but it could be said only by means of gradual "climbing up." The same held true of the street address.

For patients with word-deafness, the more automatic parts of speech, such as prepositions, adjectives, etc., are easier to use than nouns. Some individuals can say what they wish if they "say it at once." At times words are uttered automatically as in the singing of a song. Gowers suggests that when the left hemisphere is involved, the automatic revival of words is probably made possible by the centers in the right side of the brain, and he states that "the slow recovery of the power of comprehension of spoken words is by the 're-education' of the right hemisphere, since such regained power has been again lost in right-sided disease."

Recovery from sensory aphasia seems easier than from motor aphasia.

Pure *word-blindness* (alexia), which is produced by a lesion in the angular gyrus, is not common. The symptoms are inability to read print although it is clearly seen, and although the patient continues to write, talk, and understand spoken words well. He cannot copy satisfactorily. Some suffer from hemianopsia, and contralateral hemi-anesthesia or paresthesia. There is seldom any motor weakness. The intelligence is preserved.

The most common type of aphasia is the *mixed* (frontolenticular, lenticular zone aphasia). It is evidenced by total or marked loss of voluntary speech (aphemia), impairment of the ability to read, difficult comprehension of spoken words, and, as a rule, by marked hemiplegia without loss of sensation. It results usually from hemorrhage from the branch of the middle cerebral artery which supplies the corpus striatum and internal capsule of the left side, and involves the lenticular zone of Marie and some of the fibers from the frontal and temporal lobes.

So-called *global aphasia*, which involves all parts of speech, is caused by a lesion of the left gyrus supramarginalis. It is associated with apraxia or "inability to perform certain acts, where no paralysis prevents their execution. . . ." According to Foix *apraxia* is of three kinds: the motor, which is usually unilateral, right-sided, and renders the patient unable to imitate the voluntary movements necessary to perform such an act as brushing the hair when he is given the brush and asked to use it; the ideational (sometimes called *agnosia*), which seems to destroy the idea of how to perform an act alone although imitation is possible; and the ideomotor,

which is a combination of these two, and is characterized by loss of the idea of the act to be performed and by awkwardness in attempting to perform it.

Examination of an Aphasic Patient.—In an aphasic patient the general neurological examination is of great importance, because it often aids directly in determining whether the lesion is on the right or left side of the brain, and whether it is situated in the frontal, temporal, parietal, or occipital lobe. In some individuals exact localization of the abnormality depends entirely, however, on the type of speech disturbance. The following points are of great importance in the diagnosis of aphasia and should be carefully observed by the physician:

Is the patient right- or left-handed, and is he of right- or left-handed stock?

How much voluntary speech is retained, what are the defects in pronunciation, and is the speech jargon?

If there is little or no voluntary speech, is it possible to express ideas or emotions by pantomime or gesture?

Can the patient write voluntarily and to dictation?

Can he calculate or solve simple arithmetical problems?

Can he hum a tune or sing a song?

Can he understand spoken language and obey simple commands, such as to bend the right thumb, or to touch the right ear with the left thumb?

As commands increase in difficulty or abstractedness is it possible for the patient to obey them? For example, can he on request take your pen and pencil, place the pencil on his table, and return the pen to you?

Can he name a series of common objects (pen, pencil, penny, handkerchief, note-book, key, box of matches, the colors of different cards) which are placed in front of him, and can he write the names of them as they are presented to him?

Does he appreciate their use?

Can he choose from a group of objects those for which you ask?

Can he correlate the printed name of an object with the object itself?

Does he understand the meaning of gestures? (Pretend you are going to hit him.)

Can he read aloud and silently, and can he repeat the substance of what he has read?

The degree of symbolic thinking and expression retained may be further tested by means of jig-saw puzzles, games of cards (bridge or poker), drawing both voluntarily and to command, copying objects, making a plan of a well-known room, telling time, and placing the hands of a clock in certain positions at command.

Treatment.—In addition to removal of the cause of aphasia, the treatment consists in re-education. Patient work under guidance often allows the subject to acquire a satisfactory vocabulary again. Whether this is accomplished by vicarious activity of centers in the right side of the brain or not seems to make no difference in recovery of the function of speech. Teachers accustomed to educate deaf and dumb children by the oral and lip-reading method are often very successful in such therapy.

Lewis Stevenson.

Reference

Head: Hughlings Jackson Lecture for 1920; Brain, 1920, 1923.

AFFECTIONS OF THE BLOOD-VESSELS OF THE BRAIN

Cerebral Arteriosclerosis.—Arteriosclerosis of the brain may be part of a generalized arteriosclerosis or definitely limited to the cerebral vessels.

Symptoms.—The symptoms of arteriosclerosis of the brain are varied. There may be mild dizziness or severe syncopal attacks; occasionally nausea or vomiting which may lead to the erroneous diagnosis of "indigestion"; transitory paralysis of one side; or fleeting aphasia. Multiple small foci of softening may lead to intellectual deterioration or even obvious dementia; they often produce the syndrome of *pseudobulbar paralysis* with dysarthria, small-step gait, emotional instability, and salivary drooling.

Epilepsy may also be a symptom, in fact many cases of epilepsy coming on late in life are caused by cerebral arteriosclerosis. Mild types of arteriosclerotic disease of the brain appear under the guise of *neurasthenia*. There may be severe vertigo which resists treatment or occurs in episodes; headache; mild delirium; disorientation; inability to concentrate; or a syndrome resembling Korsakoff's psychosis. In all these cases it is very important to look for changes in the retinal arteries.

Often well-developed arteriosclerosis of the brain causes no cerebral lesions or symptoms during life, and the patient may retain his full mental vigor. In most cases, however, there is atrophy of the convolutions, thickening of the meninges and cortical vessels, and an increase in the glia. The patient exhibits emotional instability, impairment of memory, and various phases of mental deterioration. Some individuals become irritable, highly emotional, suspicious, and slovenly; indeed, the personality may completely change. The writer has observed great sexual hyperactivity in a man of seventy-five.

There are special types of arteriosclerosis of the brain. In the *presbyophrenia of Wernicke* there is a tendency to fabrication and disturbance in memory with preservation of thought and judgment. The *Binswanger form of presenile dementia* is characterized by loss of memory and mental hebetude; *Alzheimer's disease*, by progressive dementia, aphasia, and, at times, focal symptoms.

Treatment.—The treatment is largely prophylactic. Avoidance of physical or mental overexertion, and the institution of rest-cures at home or in a sanatorium provide psychic rest and physical relaxation. Graduated exercises may be tried, but should be so regulated that the patient can rest for part of the day. In the severe types complete cessation from work may be necessary. Patients should be warned against straining at stool. Sexual activity must be limited. The diet need not be restricted to milk and vegetables, but excessive consumption of meat cannot be permitted. Curtailment of the salt intake is desirable. The meals ought to be small and taken with as little fluid as possible. The patient should not be permitted to gain weight, in fact, should reduce slightly. Alcohol, coffee, and tobacco must not be used. Mineral oil or mild cathartics may be given to regulate the bowels. Warm baths and other forms of hydrotherapy are beneficial, particularly for patients with nervous symptoms. Nauheim baths also are of service. Cold baths should be avoided. For the headache and vertigo, which frequently are troublesome, hot fomentations may be applied to the forehead and neck. Mild massage is also of value. The high-frequency current has its uses.

Iodids, which still play the chief rôle in the medical treatment, are said to delay the advance of the disease. They may be administered in the form of sodium or potassium iodid (gr. 5 three times a day after meals) or as sajodin (gm. 0.5 three or four times a day). Occasional doses of diuretin

(gr. 8 two or three times a day) may be of service. Nitrites have been recommended to reduce hypertension. In neurotic individuals, bromids seem to relieve the headache, vertigo, insomnia, and excitement. For arteriosclerotic epilepsy, luminal ($\frac{1}{2}$ gr. twice a day) is a great aid; for the insomnia, either veronal or medinal (gr. 5 to 10) may be given before retiring. Antineuralgic remedies may be employed for headache. Treatment should also be devised for the accompanying nephritis and hypertension.

Circulatory Changes in the Brain.—Our knowledge of circulatory changes in the brain is incomplete. Data are for the most part obtained during fainting spells or when the patient is plethoric. Experiments have demonstrated, however, that a sudden, large loss of blood or the acute shutting off of the cerebral circulation usually produces coma and convulsions. In dogs, simultaneous ligation of the carotid and vertebral arteries produces idiocy associated with definite changes in the nerve-cells of the cortex.

Anemia of the brain becomes manifest after severe hemorrhage, the aspiration of a large quantity of ascitic fluid, in acute cardiac weakness, and in spasm of the cerebral blood-vessels. The best example of an acute cerebral anemia is that resulting from the rupture of an ectopic pregnancy. The face and mucous membranes are pale; the patient complains of blackness before the eyes; there is clouding of consciousness; and the gait becomes unsteady. The patient experiences buzzing in the ears and nausea, frequently vomits, is apathetic, and drowsy. The pupils are small. The syndrome resembles sleep. Great loss of blood is followed by coma, marked dilatation of the pupils, and frequent convulsions.

Mild hemorrhage simply produces "faintness." The patient "loses his senses," yawns a good deal, and shows cold perspiration and pallor of the skin and mucous membranes. The pulse becomes rapid, the respiration sighing and irregular. There are no convulsions. The syncope may last from a few minutes to an hour. Consciousness returns when the patient is made to lie down.

Fainting may result from fear, sorrow, the sight of blood, or severe pain. Neuropathic individuals faint easily. There may be a hereditary predisposition to syncope.

Chronic anemia is associated with chlorosis, pernicious anemia, leukemia, and bleeding hemorrhoids. It is manifested by pressure in the head, drowsiness, apathy, vertigo, tendency to faintness, impairment of memory, and Korsakoff-like phenomena. In some cases a change may be noted in the circulation of the retinal vessels. The symptoms are usually worse when the patient is erect. The delirium of inanition may be due to cerebral anemia. Severe diarrhea may evoke similar symptoms (hydrencephaloid state of Marshall Hall). A general spasm in the cerebral vessels may result in cerebral anemia.

Prognosis.—Mild attacks of cerebral anemia are rarely dangerous. Severe hemorrhage with repeated convulsions may prove fatal. Dilatation and fixation of the pupils is usually an ominous sign. Primary optic atrophy, aphasia, or hemianopsia may follow severe hemorrhage.

Treatment.—In the acute cases, after checking the hemorrhage, the patient is placed in the recumbent position. The extremities are bandaged tightly and elevated, to supply blood to the heart. Heat is applied. Stimu-

lants such as caffein or hot coffee may be administered. Amyl nitrite is sometimes of value. Artificial respiration, transfusion, or saline infusions are powerful aids.

Hyperemia.—Cerebral hyperemia may be active or passive. The possibility of permanent overfilling of the brain with arterial blood is doubtful, but hyperemia may occur in plethoric individuals of diminutive stature with short necks. It is manifested by ready suffusion of the face after meals or after exertion, and is often associated with increased blood-pressure and congestion of the head. The patient has a subjective sense of warmth with redness of the face, and speaks of throbbing of the temples, spots before the eyes, headache and vertigo. There is usually slight clouding of consciousness; while in more severe conditions there may be confusion and even manic excitement.

Apoplectiform seizures with transitory paralysis may occur. Amyl nitrite has been known to produce a temporary aphasia due to cerebral congestion in part dependent on disturbed vasomotor tone. A tendency to congestion of the brain is frequently observed in psychoneurotics. Onanism may be an etiological factor in such cases. Oppenheim has observed the association of cerebral symptoms with stubborn constipation. Among the other causes of cerebral hyperemia may be mentioned the contraction of the peripheral blood-vessels after a cold bath, and suppression of menses. The exacerbation of migraine with each menstrual period may be due to cerebral congestion or hydremia. Augmentation of the blood supply to the head may also result from dilatation of the cerebral blood-vessels.

Passive hyperemia is usually a chronic condition due to interference with the venous outflow by tumors in the neck; thyroid enlargement; compression of the superior vena cava by mediastinal tumors; cardiac decompensation; or emphysema. Pulmonary abnormalities which increase the intrabronchial pressure may also play an etiological rôle by interfering with the return flow of blood to the thorax.

Symptoms.—The symptoms are drowsiness, headache aggravated by coughing, vertigo, and confusion. They become worse when the patient lies down. Cyanosis of the mucous membranes and face is usually noticeable.

Prognosis.—The prognosis of simple congestion of the brain is unfavorable only if there is antecedent organic disease of the heart or blood-vessels. The apoplectiform habitus already described predisposes to cerebral hemorrhage.

Treatment.—The treatment is largely symptomatic, and consists of catharsis and the relief of headache and insomnia by administration of mild narcotics (bromids and chloral). Lesions of the superior mediastinum (substernal struma) may be helped by surgery. All forms of physical and mental exertion are to be avoided; the use of strong coffee and tea is best interdicted; alcohol should not be taken. Warm foot-baths are of value. During the attack the patient must be made to sit up. The room should not be too warm. Application of mustard to the neck, chest, or lower extremities frequently gives relief. In severe cases, particularly in plethoric individuals, venesection, vigorous catharsis, and hot foot-baths are necessary. For cardiac decompensation it may be desirable to give digitalis.

Cerebral edema is not a clinical entity, but is associated with "serous

meningitis" or cerebral atrophy. In many cases of cerebral congestion the blood-vessels are distended and the brain contains extra moisture. This is often seen in uremia and in alcoholic intoxication, and may occur in trauma. It sometimes is secondary to the formation of tumors or abscesses, and under these conditions renders the brain anemic and glistening. Some degree of internal hydrocephalus is usually present. The symptoms are those of the underlying condition. Uremic paralysis and convulsions have been ascribed to this edema of the brain.

Cerebral Hemorrhage.—Incidence.—Hemorrhage into the brain is one of the commonest cerebral accidents. Although it usually occurs in later life (after the age of forty) it can occur at any age. It is more common in men than in women. The hemorrhage almost always results from vascular disease—particularly from atherosclerosis, and usually follows rupture of some of the branches of the circle of Willis—most often of the branches of the Sylvian artery (middle cerebral). The rupture usually takes place in the wall of a miliary aneurysm, but occasionally in the wall of a so-called mycotic aneurysm. The latter lesion is especially common in children with infective endocarditis.

Etiology.—The causes of vascular disease of the brain are manifold: among the most common are advancing age, gout, intoxications (alcohol, lead, tobacco, diabetes), and infections such as syphilis. In lues, thrombosis occurs more often than hemorrhage. Acute infectious diseases (typhus and scarlet fever) also occasionally cause cerebral bleeding. At times the hemorrhage is an incident in hemorrhagic diathesis (purpura, pernicious anemia, and leukemia). Chronic interstitial nephritis with its associated hypertension increases the danger of bleeding. There may be a familial tendency to cerebral hemorrhage.

The immediate cause of hemorrhage is a rapid rise in blood-pressure as a result of severe muscular exertion, coughing, sneezing, straining at stool, coitus, parturition, or vomiting. In children, whooping-cough, severe mental excitement, and fear may be the precipitating factors. Trauma may act as an exciting cause in the presence of already damaged vessels. According to Volkmann, a pressure fourteen times the normal is required to rupture the healthy carotid artery.

Morbid Anatomy.—Certain areas of the brain show a predilection for hemorrhage, *i. e.*, the region in or near the basal ganglia (including the corpus striatum, optic thalamus, and the adjacent part of the capsule), the centrum semiovale, the cortex, and the pons. Cerebellar hemorrhage is rare.

Miliary aneurysms seldom develop in the arteries of the basal ganglia, but sclerosis may become advanced. The lenticulostriate and the lenticulo-optic branches of the Sylvian artery are those most commonly involved. The lesion may attain a diameter of 1 mm. At first only the muscular coat atrophies; later all the coats undergo degeneration and dilatation, with consequent, imminent danger of hemorrhage.

The size of hemorrhage varies. The blood may plough through the brain tissue and perforate into the ventricles. The largest foci are usually in the basal ganglia and centrum semiovale; those in the cortex and pons are much smaller. Their color and nature varies with the age of the hemorrhage; when fresh they have the color and consistency of coagulated blood; later they may turn brownish-black, brown, or even yellow; after the fifth week the yellowish color becomes more and more evident.

At least four weeks are necessary for the formation of an apoplectic cyst. In the adjacent brain substance proliferation of the glia precedes the formation of true connective tissue. The contents of the focus are slowly absorbed until only a hollow cavity remains. This is later filled with yellowish fluid. When the hemorrhage is extensive and causes immediate death, the convolutions are flattened and the sulci narrowed.

Symptoms.—*Apoplectic Seizure.*—The symptoms are both acute and chronic in character. The immediate sequel of cerebral hemorrhage is the apoplectic seizure which leads to persistent paralysis and usually to hemiplegia. Although most patients can be found to have had either *premonitory symptoms*, such as dizziness, a sense of pressure in the head, paresthesia in one-half of the body, anxiety, confusion, and disturbances of speech, or a history of high blood-pressure, arteriosclerosis, and pathological urinary changes, the apoplectic seizure may suddenly occur in an individual in apparently perfect health. Epistaxis or retinal hemorrhage sometimes precedes the acute manifestation. *At the onset* the patient may fall suddenly to the ground and become unconscious (fulminating apoplexy); may vomit; or may suffer merely a clouding of consciousness or temporary vertigo. The clinical variations depend upon the size, rapidity, and site of the hemorrhage. Bleeding into the cerebellum and pons is less frequently associated with disturbances in consciousness.

During the height of the attack the patient is comatose and cannot be roused. The face is flushed and puffy; the pupils do not react to light, and may be normal in size or dilated; the corneal reflexes are abolished bilaterally; the extremities are limp; and both deep and superficial reflexes are absent. The pulse is full and bounding, at times rapid. Breathing is slow, deep, and often stertorous because respiration sets the flabby palate and vocal cords in vibration; at times it is of the Cheyne-Stokes type. The cheeks are often puffed out, most markedly on the paralyzed side. The patient cannot even swallow fluids. There is incontinence of urine and feces, and occasionally retention. The urine contains albumin and often sugar. There may be generalized or unilateral convulsions. Fever usually develops after the attack and if high is of serious import.

The apoplectic seizure may last from several hours to several days. The causes of coma are the circulatory disturbance in the brain, the pressure of the exudate, and occasionally diaschisis.

In many cases there is conjugate deviation of the eyes. A mild papilloedema may be observed, usually on the side of the lesion. If death does not result the patient gradually regains consciousness and exhibits a hemiplegia. As he emerges from coma the reflexes return and, in spite of continued somnolence, swallowing is possible. There is some return of active motion. Asymmetry of the face is noticeable with sagging of the angle of the mouth on the affected side; the palpebral fissure is wider than normal, the nasolabial fold less marked, and the patient drools on the paralyzed side. The muscle tonus is increased. Cremasteric and abdominal reflexes on the paralyzed side are absent. The Babinski sign is positive, and the Oppenheim and Mendel reflexes as well. In respiration the involved side of the chest lags, and the diaphragm also functions poorly. If there is conjugate deviation of the eyes, the hemorrhage is usually situated on the side toward which the head and eyes are directed. "Patient looks at his lesion." Hemiplegia is often accompanied by vasomotor disturbances,

such as edema of the involved hand. The pain, which may be felt on the paralyzed side, is either arthritic or central (thalamic). In conditions complicated by heart disease or nephritis the edema may be more marked on the affected side. When there has been no apoplectic manifestation paralysis may be the first symptom. The patient notes that he cannot hold or grasp things as well as previously or his leg may give way under him.

Hemiplegia.—The typical result of the apoplectic seizure is hemiplegia, *i. e.*, paralysis of the arm, leg, face, and tongue on one side of the body. For a short period after the seizure sensation is disturbed, that associated with the posterior column or of the gnostic type, *i. e.*, the perception of vibration, joint movements, and two point discrimination, more markedly than pain and temperature perception. Speech is dysarthric and indistinct. If the internal capsule is directly involved in the hemorrhage and more or less destroyed, hemiplegia remains as a direct focal symptom. Later on the picture changes somewhat. There is marked increase of the deep reflexes on the paralyzed side, and sometimes a tendency to ankle-clonus. After several weeks a certain amount of mobility returns on the involved side, probably because of the functioning of accessory motor pathways. The arm usually remains paretic for a longer period. The leg is held in extension; the arm may recover some power, more proximally than distally. The extensors of the hand and fingers seem to be most involved, those of the thumb most severely. The flexors of the knee and extensors of the feet and toes are most apt to remain permanently impaired. Hemiplegic patients regain power slowly and can usually walk after six to eight weeks.

After a time the *muscle tonus* increases and contractures develop, most markedly in the arm. The upper arm is adducted, the forearm flexed at an angle, with the hand pronated and flexed, and the fingers flexed tensely. The leg usually becomes fixed in extension. The contraction of the gastrocnemius group leads to the formation of pes equinus or pes equinovarus and produces considerable difficulty in walking. The patient, therefore, supports himself on his sound leg and by circumduction lifts the paralyzed leg from the ground and swings it in an arc with the healthy limb as the axis. Sometimes the permanent paralysis is flaccid, a condition which, according to Oppenheim, results from very extensive disease of both the motor and sensory pathways. In the author's experience the incidence of rigidity seems to depend on the proximity of the lesion to the basal ganglia. The musculature usually remains intact or there may be some atrophy from inactivity. There are, however, no changes in electrical irritability.

If the hemorrhage extends to the posterior limb of the internal capsule or into the optic thalamus, there occurs in addition to the hemiplegia a *hemianesthesia*. All forms of sensation are diminished or lost, touch being most involved. The sensory changes may be limited to the distal parts of the extremities. Hemiataxia may result from loss of deep muscle sensation.

A certain amount of *mental disturbance* follows cerebral hemorrhage. There is diminution of intelligence, irritability, and disturbance of memory. Real dementia develops only when cerebral softening takes place because of generalized atherosclerosis or lues. The involved limbs may be unduly warm or cold and cyanotic. Trophic changes in the joints have been

described (Charcot). In right-handed individuals, if the hemorrhage involves the basal ganglia and subcortical pathways of association on the left side, there may be aphasia. The more extensive the hemorrhage and the more it damages the speech center, the more permanent the aphasia. When the hemorrhage bursts into the ventricles and reaches all chambers of the brain as it occasionally does, the paralysis spreads to all the extremities. Convulsions may ensue, but more often generalized rigidity of one or both sides develops. The pulse is slowed. The temperature falls. There are marked respiratory difficulties. Lumbar puncture releases bloody fluid. This hemocephalus usually proves fatal within twenty-four hours.

Hemorrhage into the pons and medulla may be bilateral or unilateral, and may involve the tegmentum. Usually with bleeding into the pons the apoplexy is manifested only by vertigo. The most common objective sign is the alternating hemiplegia (homolateral cranial nerve palsy, contralateral hemiplegia). The paralysis is usually associated with disturbances in articulation and deglutition. The pupils are usually narrow, often fixed. The third cranial nerve, the motor fifth, and the sensory fifth may also be involved. General convulsions may occur. Opisthotonus is not uncommon. Respiration is often seriously disturbed. Hemorrhage into the pons may evoke symptoms of acute bulbar paralysis, but these are much more frequently associated with apoplexy of the medulla. Cerebellar hemorrhage leads to cerebellar ataxia, vertigo, and vomiting.

Differential Diagnosis.—The differential diagnosis of apoplexy is of great importance. The condition must be distinguished from simple fainting, epilepsy, uremia, and the coma caused by intoxication. *Simple fainting* can easily be distinguished by the absence of a profound loss of consciousness and by its shorter duration. The pulse is usually more rapid and feeble. The fainting person is pale, but not comatose. The *epileptic seizure* is indicated by tongue bite, scarring of the tongue from previous seizures, and the absence of hemiplegic phenomena. Epilepsy is much more common in younger individuals. *Attacks of hysteria* are easily eliminated by retention of the pupillary and corneal reflexes and the presence of normal deep reflexes. The general attitude of the patient is quite different from that of the apoplectic individual. The face and tongue are rarely involved. The Babinski sign is absent. Abdominal reflexes are retained. The hysterical hemiplegia is also accompanied by a characteristic hemianesthesia. The attack can be brought on by pressure over the ovary through abdominal or through vaginal examination. The disturbance yields readily to psychotherapy. *Uremic coma* can be differentiated by the presence of albumin and casts in the urine, the demonstration of edema, albuminuric retinitis, the history of headache, vomiting, and asthmatic attacks, and the study of the blood chemistry. *Diabetic coma* can also be ruled out by examination of the urine and the demonstration of acidosis (acetone odor in the breath, low CO_2 content of blood). *Alcoholic coma* can be detected by the odor of alcohol, the tendency to delirium, and motor restlessness. Morphin intoxication renders the pupils typically miotic. *Acute hemorrhagic encephalitis* is also associated with clouding of consciousness, but is usually preceded by headache and fever. The coma is less profound and the reflexes are often retained. In apoplexy without very profound coma the corneal reflex is diminished or abolished on the side of the hemiplegia. This unilateral diminution or abolition of the reflex is

often of great value in differentiating the coma due to apoplexy from that dependent on other causes. The differentiation of cerebral hemorrhage and softening from *embolism* or *thrombosis* is not always easy. Hemorrhage is rare before forty; embolism is most common in children; and thrombosis usually occurs in middle life. Cardiac lesions suggest embolism; arteriosclerosis indicates thrombosis, and so also does syphilitic infection. Simultaneous hypertrophy of the left ventricle and nephritis would point to hemorrhage. The history of recent rheumatism even without endocarditis suggests embolism. Redness and puffiness of the face and a full and strong pulse should arouse suspicion of hemorrhage. Most apoplectic patients exhibit hypertension. The coma of hemorrhage is deep and persistent. Premonitory symptoms such as paresthesias, transitory weakness of one side, and intermittent disturbances in speech favor a diagnosis of softening or thrombosis. With embolism, preliminary symptoms are unusual. Repetition of the vascular injury is probably evidence of softening. Infarction in other organs suggests embolism. The absence of loss of consciousness, and the appearance of symptoms indicating an extensive lesion, point to softening. The incidence of phenomena of motor irritation, especially of Jacksonian seizures, is higher in embolism and thrombosis.

The symptoms of *cerebral tumor* may be simulated by focal signs due to an arteriosclerotic cyst.

Hemorrhage into a hitherto *latent neoplasm* may simulate thrombosis. The onset of a metastatic neoplasm of the brain may resemble a vascular accident. There have been reported cases of transitory hemiplegia resulting from *cerebral vascular spasm*. The condition is allied to intermittent claudication of the lower extremities. These "vascular crises," as they have been termed by Pal, are particularly common in smokers.

Prognosis.—The apoplexy may rapidly cause death, particularly when the hemorrhage is extensive and perforates into the ventricle. If the coma persists more than twenty-four hours or deepens constantly there is grave danger to life. A steady fall or an unusual rise in temperature is also of serious import. *Decubitus acutus* and Cheyne-Stokes breathing are unfavorable manifestations. Hemorrhage into the pons and medulla is frequently fatal. Secondary aspiration or hypostatic pneumonia is a frequent cause of death. After the occurrence of hemiplegia symptoms diminish in severity; the less complete the apoplectic attack, the better is the outlook, although a small hemorrhage in the region of the motor tract may evoke permanent unilateral paralysis. Careful observation of the symptoms during the first week is necessary. If the hemiplegia persists unchanged for a month or more, it is usually due to invasion of the motor tract and recovery is unlikely. If, on the other hand, muscular power returns somewhat, during the first few days, the prognosis is much better. The character of the reflexes does not seem to be significant. The presence of contractures is of serious import. Most aphasias associated with hemiplegia seem to improve, although frequently only after considerable time, and often only partially. Hemianopsia is also apt to be permanent. The rapid subsidence of paralysis within a few days, particularly in a young adult without hypertension, suggests very strongly that the attack is the first episode in general paresis. This need disturb neither the intelligence, pupillary reaction, nor speech, but the serological reactions characteristic of syphilis can usually be evoked.

It may take the subject three or four months to regain the power of locomotion with the patient help of the physician and family. The prognosis for patients who have sustained a cerebral hemorrhage is uncertain because the etiological condition still persists. Fifteen to twenty years may elapse between the first apoplectic attack and that which causes death.

Treatment.—The treatment is *first prophylactic, i. e.*, that of the underlying vascular disease. The patient should avoid liquor and tobacco, and, if adipose, receive a diet carefully regulated to allow reduction of weight. For the underlying arteriosclerosis, iodids (potassium or sodium iodid 0.3 to 0.9 gm.) and sajodin (0.5 gm. three times a day, after meals) are useful even in the non-syphilitic cases. Some observers advise reduction of the calcium intake, while others favor the administration of milk. About restriction of salt and purins there seems to be general agreement. Highly seasoned foods are undesirable. The patient should be instructed to avoid everything that suddenly elevates the blood-pressure, *i. e.*, straining at stool, sexual intercourse, the carrying of heavy weights, undue physical exertion, and mental excitement. A sojourn in a warm climate often helps the underlying sclerosis and hypertension. During the acute apoplectic attack when diagnosis of hemorrhage or softening has not been made, the following therapy may be employed: The patient should be put to bed in a room free from noise with the head elevated. If he has fallen to the ground the clothing must be loosened around the neck. Difficulty in swallowing contraindicates the administration of nourishment by mouth. An enema may be given. When the face is puffy, the pulse full and strong, and there is reason to suspect hemorrhage, venesection is advisable. It should be employed only for plethoric individuals, not for patients who seem asthenic or arouse suspicion of thrombosis. Usually 250 to 300 c.c. of blood are removed. No attempt should be made to arouse the patient. For those with stertorous breathing the prone position is better. If the tongue tends to fall back into the throat it should be held forward. Attempts to treat the hemorrhage surgically have produced no striking results. If there is definite hemorrhage, an ice-bag may be placed over the site of the lesion. Unless there is special need, it is best during the first few days to avoid medication. For restlessness, bromids may be tried. If there is much headache or sleeplessness, an opiate or some other mild soporific should be administered. If there is reason to suspect lues, mercury and salvarsan must be administered at once. In uremia, lumbar puncture is often helpful. The attendant should guard against the development of decubitus. The tendency to pulmonary congestion should be counteracted by frequent shifting of the patient from side to side.

Treatment of the hemiplegia itself includes general massage of the paralyzed limbs and passive exercise. In order to avoid contractures and joint changes, such therapy may be instituted in the second week of illness. After two or three weeks electrical treatment (mild faradic current) may be employed. The electrical stimulation is best applied to the antagonists of the contracted muscles several times daily for four or five weeks. Sometimes surgical measures such as tenotomy and muscle transplantation have been employed. The patient should make no effort to walk for three weeks, and even then must spend the major part of the day in bed. Movements of locomotion may be carried out while he is sitting in a chair or lying down.

If dependent limbs are cold and cyanotic support is helpful. Massage and passive motion should be continued. Aphasia requires adequate re-education. Warm baths are frequently useful. The patient should be instructed to lead a more or less sedentary life in order to avoid further attacks.

Cerebral Softening (*Encephalomalacia*).—Etiology.—Softening of the brain is caused by occlusion of an artery with resulting tissue ischemia, and degeneration of the area of the brain deprived of nourishment. Blocking of the vessel may follow either embolism or thrombosis. *Embolism* takes place in chronic valvular disease (particularly in mitral stenosis), or in the auricular thrombosis consequent to dilatation of the heart. Occasionally the embolus originates in the aorta, and in chronic suppuration of the lung it may come from the pulmonary veins. Sometimes tumors of the heart, lungs, or other organs produce metastatic occlusion of the cerebral blood-vessels. The embolus may also be derived from a thrombus in one of the larger cerebral blood-vessels.

Thrombosis of the cerebral blood-vessels is usually the result of arteriosclerosis or specific endarteritis. Disease of the blood-vessels may be produced by chronic intoxications (lead, tobacco, etc.) or may be a result of hereditary weakness of the arterial tree. Oppenheim thought that those psychoneuroses which were associated with symptoms referable to the cardiovascular apparatus often led to atherosclerosis early in life. Laborers are also particularly prone to cerebral vascular changes.

Certain diseases are said to increase the coagulability of the blood and thus produce thrombosis although the vessel walls are normal. In this category are included infectious diseases (typhus, scarlet fever) and the puerperal state. Thrombosis is said to be more common in individuals with cardiac weakness because of the circulatory retardation. Chlorosis and leukemia may also be causes, the former probably on account of the associated hypoplasia of the cardiovascular system. Carbon-monoxid poisoning often produces softening, particularly in the lenticular nucleus. In some cases of tubercular meningitis, thromboses caused by proliferative vascular changes have been observed. Both embolism and thrombosis occur as the result of some precipitating factor such as fear, excitement, physical exertion, or parturition. The embolus usually remains at the bifurcation of large vessels into branches.

Morbid Anatomy.—The Sylvian artery (middle cerebral) and its branches, especially on the left side, are most commonly involved; and the left vertebral artery is also frequently affected. Thrombosis occurs principally in the large vessels at the base of the brain. Embolism may lead to secondary clotting of the blood in the neighboring vessels. Occasionally there may be absorption or recanalization of the thrombus. In endarteritis the entire lumen of the vessel may be obliterated over a large area. The vessels descending from the cortex into the brain substance and white matter are commonly end-arteries. In the cortex of the brain, collateral circulation is more readily established than in the brain stem. Therefore occlusion of the Sylvian artery, for instance, may not result in softening of the cortex, while the deeper structures may be the seat of extensive degeneration. According to Monakow, occlusion of the main trunk of the middle cerebral (Sylvian) artery leads to softening of the entire lenticular nucleus, the anterior part of the optic thalamus, the subthalamic

region, the motor area, the island of Reil, and the third frontal convolution. Occlusion of the posterior cerebral artery evokes softening of the occipital lobe, the calcarine area, the cuneus, and the posterior part of the optic thalamus.

Softening may be found in all parts of the brain, but most often in the cortex. The caudate nucleus and putamen are also frequently affected. Lesions are rare in the cerebellum. The process of softening does not result immediately upon occlusion of the vessels, but may be delayed two or three days. As soon as the brain assumes the characteristic consistency, serous infiltration of the involved area takes place rapidly.

Softening is of three types—red, yellow, and white; the color depends on the blood content of the tissue. Red softening is particularly common in the cortex because of the rich blood supply, and may also be frequently seen in the central gray matter near the aqueduct of Sylvius. After a few weeks, fatty changes in the diseased tissues and degeneration of the blood-pigment render these red, softened lesions yellowish. In the white matter the softening usually assumes a whitish or bluish-white color, and contains droplets of myelin, detritus, and granular cells. These characteristics distinguish true softening from postmortem maceration.

After absorption of the degenerated material a cyst remains and at times scarring. This is particularly noticeable in the cortex, which may become mouse-eaten in appearance in arteriosclerotic patients. The size of the softened areas varies from that of a pin-head to that of a fist. An entire hemisphere may undergo softening, for example, after thrombosis of the carotid. At times cerebral embolism may be associated with embolism of the central artery of the retina.

Embolism occurs most commonly in young adults, while thrombosis exclusive of the syphilitic type is seen chiefly in old patients.

The thrombosis involving the basal ganglia, chiefly the lenticular nucleus, is described as the lacunar type and leads to a clinical syndrome very much like paralysis agitans.

Symptoms.—In cases with large areas of softening, particularly those due to embolism, the *onset* is apoplectiform. Embolism and thrombosis of the smaller vessels may occur without loss of consciousness. If consciousness is lost, the coma is not profound and is briefer than that produced by hemorrhage. It may be followed after several days by a rise in temperature, and in septic conditions by chills and fever. Embolism of a large trunk always produces loss of consciousness, either because of mechanical injury to the brain or because of so-called diaschisis. The vascular occlusion may also be manifested by a convulsion. Vomiting is a symptom, and occasionally there is considerable prostration and mild delirium.

Thrombosis of the principal vessels also may begin with apoplectiform symptoms, but the loss of consciousness is usually less profound. At times the paralysis develops very quickly. There may be only a period of transitory confusion or mild disturbance of cerebration. In some instances the patient complains simply of headache and vertigo. In embolism there are no premonitory symptoms, while in thrombosis these are usually present and vary with the extent of the underlying arteriosclerosis. The prodromata include pressure in the head, and headache intensified by coughing, sneezing, straining at stool, or lying down, as well as disturbances in memory and intelligence, mild confusion and excitement, or transitory aphasia.

Many patients suffer from sleeplessness, exhaustion, loss of interest and ambition, emotional dulness, irritability, tendency to weep, transitory paresthesias, and paralysis.

The characteristic *result of cerebral softening* is the *hemiplegia*, which is often progressive. The first mild hemiparesis is followed by increasing weakness. At first only one limb may be involved, later the entire side. In right-handed individuals the motor phenomena are associated with aphasia. When the area of softening is very circumscribed either a monoplegia with aphasia, aphasia alone, or hemianopsia ensue. Indirect local signs may result from diaschisis.[1] In such cases the paralysis may be an indirect symptom and the motor phenomena may disappear. Hemianesthesia may accompany the hemiplegia, exist alone, or be associated with hemiataxia. The hemiplegia may disappear because of the establishment of a collateral circulation or the relaxation of angiospasm.

Occlusion of the internal carotid, especially if the anterior cerebral and the Sylvian artery are involved, produces very extensive softening with hemiplegia, and profound coma leading rapidly to death. Occlusion of the main branch of the Sylvian artery causes hemiplegia with permanent or transitory hemianesthesia and aphasia, if it occurs on the left side in right-handed individuals. When the plugging process involves only the branches, the symptoms vary according to the area involved. In embolism, Jacksonian convulsions may precede the onset of the paralysis. Occlusion of the first branch of the Sylvian artery on the left side produces motor aphasia with facial, lingual, and sometimes brachial paralysis; of the second branch, hemiplegia or faciobrachial paralysis; of the third and fourth branches, which supply the lower parietal and upper temporal lobe, alexia and word deafness. The latter is especially noticeable after occlusion of the fifth branch. Embolism or thrombosis of the anterior cerebral artery is followed by paralysis of the leg and psychic disturbances (akinesis).[2] Occlusion of the arteries supplying the white matter gives rise to hemiplegia and hemianesthesia. Unilateral softening of the basal ganglia may produce symptoms of motor irritation and all kinds of sensory abnormalities. When the lesions are bilateral, articulation and deglutition may be disturbed, and loss of mimetic display, hyperemotionalism, bladder symptoms (basal ganglia type of pseudobulbar palsy) become evident. In such cases phenomena referable to the pyramidal tract cannot be observed.

Occlusion of the posterior cerebral arteries usually leads to hemianesthesia and hemianopsia. There are usually premonitory symptoms, such as dizziness, mental aberration, transitory hemianopsia, headache, and visual disturbances. With the acute apoplexy there may be hemiplegia with convulsive manifestations. After recession of the general symptoms the hemiplegia also disappears, but the characteristic hemianopsia remains.

Thrombosis of the basilar or vertebral artery commonly leads to acute bulbar paralysis. A fairly typical symptom-complex is produced by thrombosis of the posterior, inferior, cerebellar artery (a branch of the vertebral) which frequently has an anomalous distribution, but when blocked produces a rather characteristic syndrome. In some cases death

[1] Diaschisis is a term suggested by Monakaw for the mechanism which produces transitory symptoms of brain disease through radiation of the insult from the focus involved to adjacent areas of the brain.

[2] Akinesis denotes an inhibition of psychomotor reactions, *i. e.*, disinclination to execute voluntary acts.

with bulbar symptoms ensues rapidly, but if the patient survives the initial stage, crossed sensory paralysis (homolateral involvement of the sensory fifth and contralateral involvement of pain and temperature sense) develops with ipsolateral ataxia of cerebellar type. The innervation of the vagus and glossopharyngeus is also so disturbed that dysarthria and difficulty in deglutition occur. Sympathetic phenomena also appear on the side of the lesion. Sometimes in arteriosclerosis a number of small areas may soften, although there has been no previous major apoplectic seizure. In these cases we find disturbances in intelligence, bulbar speech, spasmodic outbursts of laughter and crying, and bladder symptoms (pseudobulbar palsy). Such softening, when fully developed, produces the syndrome of amnesia and aphasia which may go on to true senile dementia.

Diagnosis.—If the symptoms (aphasia or monoplegia) point to a focal lesion and there is no history of trauma, they are probably due to softening. The differentiation of softening of the brain and *tumor* may be very difficult, and can be accurate only after prolonged observation, particularly when the slow softening persists for a long time. In most cases of cerebral softening evidences of increased intracranial pressure cannot be found. There is no papillo-edema, slowing of the pulse, or vomiting, except with thrombosis of the basilar artery. *Localized atrophies* of the brain occurring in advanced age may simulate softening, but produce more profound coma and much more mental disturbance. *Alzheimer's disease* must also be considered. Many cases of softening of the brain without focal symptoms appear under the guise of *neurasthenia*. The patients complain of headache, vertigo, prostration, and insomnia. The constancy of the symptoms, the lack of a neuropathic history, and the signs of vascular disease, especially in the retina, will help clarify the diagnosis. Occasionally hemiplegia occurs in individuals in whose brain at postmortem examination no changes can be found. This has been observed in *tuberculosis, alcoholic intoxication, uremia, diabetes,* and *lead poisoning*. It is particularly difficult to distinguish uremic hemiplegia from that due to cerebral thrombosis, although the former is more apt to be transitory. Similar evanescent hemiplegias, which may occur in the course of *pneumonia*, have been ascribed to edema of the brain or mild meningitic changes. *Diabetes* may also be complicated by transitory hemiplegia.

Prognosis.—Death is less apt to result than after cerebral hemorrhage. Jones reports that death occurred in 30 per cent. of a series of patients with cerebral hemorrhage, in 15 per cent. of those with thrombosis, and in but 7.5 per cent. of those with embolism. Thrombosis of the basilar and carotid arteries is usually fatal. The duration of the loss of consciousness is less significant than its degree. The general condition including that of the heart is important. After localized softening the patient may live for years. If the paralytic symptoms do not improve within three or four weeks the ultimate prognosis is poor.

Treatment.—The treatment is first prophylactic, *i. e.*, that of the underlying arteriosclerosis. Venesection is not necessary in softening. For the attack itself the treatment is, with some modifications, that of hemorrhage. For cardiac weakness stimulants may be given. When there is reason to suspect a syphilitic origin of the vascular process, mercury and iodids should be administered at once and the blood and spinal fluid examined. The treatment of the paralysis has already been discussed.

Intracranial Aneurysms.—Etiology.—Syphilis is rarely the cause of intracranial aneurysms. They frequently result from embolism of the vessel wall in infectious endocarditis or from cerebral atherosclerosis, or they may be congenital. In the latter case there is frequently evidence of status thymolymphaticus.

Morbid Anatomy.—The aneurysm may be of the miliary type or may involve the large vessels. Aneurysmal dilatation is more common in the cerebral vessels than in the other arteries of the body with the exception of the aorta. The vessels most commonly involved are the arteries at the base of the brain or their branches before they penetrate the substance of the brain. The lesions are frequently multiple and are usually sacculated. Their size varies from that of a pea to that of an egg. They are more common on the left side. The adjacent parts of the brain are usually compressed or may undergo atrophy or softening.

The aneurysms usually develop in diseased blood-vessels which have lost their contractile substance in a circumscribed area. Aneurysms of the cerebral vessels are more common in early and middle life. Trauma has been said to be an etiological factor. There may be considerable softening around the sac and only a small slit demonstrable in the vessel wall.

Symptoms.—The aneurysm may produce no symptoms, or may rupture spontaneously and lead to death. There may be signs of mild cerebral hemorrhage or fulminating apoplexy due to rupture into the ventricles. The site of perforation may be so small that there is only slow oozing into the subarachnoid space. If periodic, such oozing may produce a syndrome of meningeal irritation resembling that of pachymeningitis hemorrhagica. Rupture usually follows trauma, exercise, coitus, fear, or any other condition which elevates blood-pressure. The evidence of intrameningeal bleeding is obtained by lumbar puncture. The spinal fluid is frequently slightly bloody or yellowish, on account of the presence of derivatives of blood pigment. Its cell-content may be increased. Such spinal phenomena as rigidity of the neck and positive Kernig sign may be present.

The symptoms of aneurysm are local and general. An important *general symptom* is *headache*, which is often pulsating or migrainous in character. It may be associated with vertigo and vomiting. *Papillo-edema* is, as a rule, rare. Rupture of the aneurysm directly into the sheath of the optic nerve causes *changes in the fundus of the eye*. The hemorrhage may also spread from the subarachnoid space into the optic sheath and appear under the retina.

There may be a *murmur* synchronous with the pulse, over the entire skull or over a circumscribed area; this murmur, however, is not pathognomonic of aneurysm, as it can be produced by pressure of a growth on a blood-vessel, and may also be audible over a highly vascular neoplasm. In children it has no significance because it accompanies rickets and hydrocephalus. Such murmurs can be heard in women with vasomotor disturbances, and in adults suffering from idiopathic hydrocephalus. They are also said to occur in Basedow's disease. Compression of the carotid usually abolishes them.

Although the character of the symptoms depends on the site of the aneurysm it usually suggests lesions at the base of the brain. The symptoms progress as the aneurysm increases in size or ruptures and causes hemorrhage. At times apoplectic attacks occur.

Aneurysm of the internal carotid usually affects the nerves innervating the eye muscles, the olfactory nerve, the ophthalmic division of the fifth, and the optic nerve. It may produce exophthalmos, amblyopia, and various forms of hemianopsia. There may be changes in the disks, paralysis of the oculomotor nerve, pain, and hyperesthesia or hypesthesia in the region innervated by the sensory fifth, with at times neuroparalytic keratitis. Pressure on the cavernous sinus may lead to hyperemia of the retinal veins and dilatation of the superficial veins of the face. On the left side pressure on the temporal lobe and peduncle may evoke aphasia and motor disturbances. Perforation of the aneurysm into the cavernous sinus produces pulsating exophthalmos. The aneurysm may also erode the sella turcica.

In the anterior cerebral artery an aneurysm may compress the optic and olfactory nerves. In the middle cerebral artery it may, in addition to the oculomotor, involve the olfactory nerves. The pressure is, for the most part, however, exerted on the brain substance and produces aphasia, monoplegia, or hemiplegia. Aneurysm of the posterior communicating artery may produce hemianopsia by implication of the optic tract.

Aneurysm of the basilar artery exerts pressure chiefly against the pons, medulla, or peduncle. With such a lesion, the patient usually experiences pain in the occipital region and difficulty in moving the head. Compression of the pons may be evident with symptoms of alternating subacute hemiplegia or bulbar paralysis. Manifestations of irritation or paralysis are sometimes referable to the individual cranial nerves (fifth to the twelfth). In aneurysm of the basilar artery hemiplegia shifts from one side to the other without ever disappearing completely, until finally the condition becomes diplegia or paraplegia. Vomiting and respiratory embarrassment are particularly apt to occur in these cases.

Aneurysm of the vertebral artery evokes similar symptoms, and in some individuals when the artery is dilated the palate and vocal cord on one side and the hypoglossus on the other side may be involved. The author has observed a case of aneurysm of the vertebral artery, which gave rise to the syndrome of high cervical cord tumor. Cardiac arhythmia may also be associated with the condition. In aneurysm of the posterior fossa forward flexion of the head produces respiratory disturbances.

The symptoms, according to Symonds, may be classed as local or pressure signs dependent on the localization of the aneurysm; those due to the underlying disease, and those peculiar to the aneurysm itself. *Local or pressure signs* include cavernous sinus phenomena as enumerated above. The symptoms referable to the *underlying disease* are either those of atherosclerosis or infectious endocarditis. Disturbances attributable to the aneurysm itself include leakage from the sac, meningeal irritation, and blood in the spinal fluid.

The symptoms become acute when the sac ruptures. Loss of consciousness is sometimes only slight. Blood may escape into the spinal subarachnoid space. The appearance of pain and rigidity of the neck after an apoplectic attack suggests subarachnoid rather than cerebral hemorrhage.

Diagnosis.—The history of a number of attacks of meningeal irritation is suggestive of intracranial aneurysm, especially if the spinal fluid is bloody or xanthochromic. In some patients, the syndrome of Weber is produced by an aneurysm near the crus (homolateral lesion of the third nerve and contralateral involvement of the limbs). The fever has been

ascribed to effusion into a serous cavity. "The conjunction of signs of basal meningeal hemorrhage with signs of tumor at the base is evidence in favor of aneurysm, especially if these occur during the course of arteriosclerosis or infectious endocarditis."

The diagnosis of aneurysm of the cerebral blood-vessels is extremely difficult and can usually be made only after death. Sudden development of coma with hemiplegic phenomena in young individuals without a history of syphilis or hypertension should arouse suspicion. The possibility of brain abscess must also be considered in these cases. One-third of the patients show evidence of intracranial disease.

The condition must be differentiated from *hemorrhagic pachymeningitis*, from the various types of *ophthalmoplegia*, from *migraine* with or without ophthalmoplegia, and from *tumor of the trigeminal nerve*, as well as from infectious meningitis when there is fever. If coma is marked, the disease must be distinguished from *cerebral hemorrhage*. Symptoms pointing to the region of the internal carotid (oculomotor signs or trigeminal phenomena) are highly suggestive. "If in addition we find subretinal hemorrhages, bloody or xanthochromic fluid, the diagnosis is fairly certain."

Prognosis.—The ultimate prognosis in most cases is poor. Rupture of the aneurysmal sac with subarachnoid hemorrhage constitutes the chief danger. In cases of seeping through a very small perforation there may be recovery and the patient may survive for months or even years. The prognosis depends somewhat on the primary cause. In individuals with extensive atherosclerosis or subacute endocarditis the outlook is poor. Death may rapidly follow cerebral compression.

Treatment.—Lumbar puncture may be used to drain off the escaped blood, but should not be made a universal practice because lessening the spinal pressure entails the danger of re-opening the point of perforation and re-inducing hemorrhage. It may also cause sudden death, by jamming the brain stem into the foramen magnum as it does in tumors of the posterior fossa. If the signs of cerebral compression are so severe that there is danger to life, either lumbar puncture or cisterna puncture should, nevertheless, be employed. Later on, after the acute stage when there are symptoms of meningeal irritation, lumbar puncture may relieve the pain.

Sinus Thrombosis.—Incidence.—Sinus thrombosis is rarely a primary affection, being usually secondary to phlebitis of the sinus or the veins communicating with it. This in turn is almost always the result of infectious inflammation in the vicinity of the sinus. Sinus thrombosis may, however, be non-infectious when it occurs as a sequel of extreme cardiac weakness and in marasmus. This type appears in either the very young or the very old. In very young individuals it may follow in the wake of exhaustive diarrhea, or of long-standing suppuration. The associated cardiac weakness slows the circulation sufficiently to permit coagulation of the blood. In the terminal stage of exhausting diseases like tuberculosis, carcinoma, persistent typhoid fever, and chlorosis, the contributory factors are cardiac weakness, fatty degeneration of the endothelial lining of the sinus, and an increase in the number of blood-platelets.

Secondary sinus thrombosis, which usually follows lesions near the sinus or its formative veins, is particularly common in otitis with caries of the petrous bone or the formation of cholesteatoma. It is most apt to develop in acute cases, but may come on at any time. In case of bone necrosis

there may be extensive involvement of the sinus wall, or the phlebitis may extend along veins which connect the internal ear with the sinus. It is then frequently complicated by meningitis, extradural suppuration, or brain abscess. Since the thrombosis is septic in character, the lesion extends to the jugular vein and leads to general sepsis. Sinus thrombosis may also be secondary to necrosis in other parts of the skull. It may follow septic affections of the cranium, scalp, orbit, nose, or accessory sinuses. Through the emissary veins leading inward, the cavernous sinus may be implicated by infected wounds of the face, furuncles or carbuncles, septic processes of the neck or parotid gland, and facial erysipelas.

Morbid Anatomy.—Sinus thrombosis may be localized or very extensive. In the involved sinus either a fresh grayish-red clot or an older, paler, somewhat organized thrombus adherent to the wall of the sinus may be found. The older the thrombus, the more firm the adhesion. In secondary thrombosis the process is often purulent and the wall of the sinus is greenish or greenish-yellow in color The purulent material may extend into the jugular and subclavian veins, and even into the superior vena cava. Streptococci and pneumococci have been recovered from such thrombi. There may be destruction of the wall with the formation of a perisinus abscess. The unthrombosed part of the sinus is usually very tortuous, dilated, and overfilled with blood. The parts of the brain from which the veins normally carry the blood are hyperemic, and often the site of capillary or larger hemorrhages.

In most otitic cases the lateral sinus is involved, while the superior longitudinal sinus is the most common site of marantic thrombosis. The cavernous sinus is also frequently affected. The involvement may extend from one sinus to another.

Symptoms.—The symptoms of sinus thrombosis are not characteristic. In the marantic type they are obscured by the fundamental condition; in the secondary types, by such associated complications as meningitis and abscess. Signs of venous stasis may appear, *e. g.*, in thrombosis of the cavernous sinus, there is dilatation of the frontal veins, cyanosis of the orbital region, swelling of the eyelids, chemosis, and exophthalmos. Some patients have dilatation of the retrobulbar veins, and at times papillo-edema caused by stasis in the retinal veins. There may be amblyopia. Occasionally a history of neuralgic pains in the region innervated by the ophthalmic division of the fifth nerve can be obtained. Paralysis of the eye muscles is common.

Thrombosis of the sigmoid or lateral sinus leads to edema of the soft parts in the mastoid region and swelling of the upper part of the jugular vein. Jansen found the jugular vein involved in one-third of his cases of otitic thrombosis. Sometimes a thickened cord may be palpated. The soft parts may swell because of lymphangitis near the involved vein; and the lateral movements of the head become limited, in fact there may be spasmodic torticollis. At times evidences of paralysis referable to the ninth, tenth, eleventh, and twelfth cranial nerves have been observed. If either the jugular vein or the lateral sinus be thrombosed, pressure on the jugular vein of the sound side evokes engorgement of the retinal veins. Uhthoff found ophthalmoscopic changes in about 40 per cent. of his cases of otogenic thrombosis.

Thrombosis of the superior longitudinal sinus leads to dilatation of the

veins of the frontal, parietal, and temporal regions. In some cases there is epistaxis. The fontanels may bulge. If marantic thrombosis occurs in the superior longitudinal sinus of a child, in addition to convulsions, epistaxis and visible distention of the nasal veins ensue because of the communication between this sinus and the nasal veins. In primary sinus thrombosis following chlorosis, prolonged diarrhea, or tuberculosis the onset may be acute, with violent headache, vomiting, and stupor. There may be convulsions or paralysis, and sometimes rigidity of the neck. The pulse is not typical. The patient fails rapidly and dies within a few days. The diagnosis of such a condition depends largely on the etiology and the slight signs of venous stasis. The general symptoms usually arouse suspicion of meningitis or focal disease of the brain (hemorrhage or softening in the hemisphere).

The symptoms of secondary otogenic thrombosis vary. When thrombosis of the lateral sinus occurs during chronic otitis (without sepsis or complete blocking of the vein) there are fever and headache, but these symptoms cannot be differentiated from those of meningitis, brain abscess, or extradural suppuration. Very often an extradural abscess is the etiological factor. Among the symptoms of extradural suppuration are swelling over the mastoid, pain on pressure over this area, limitation of movement of the head, and nystagmus. There may also be optic neuritis or papilloedema. The latter, however, is more common in sinus thrombosis than in extradural abscess.

Sinus thrombosis usually produces headache, vertigo, vomiting, slowing of the pulse, some rigidity of the neck, and other manifestations of meningitis. In the septic types such evidences of generalized infection as rapidity and irregularity of the pulse, chills, fever, sweats, enlargement of the spleen, diarrhea, jaundice, and metastases in the lungs and the joints are soon added to the syndrome. The blood culture is usually positive.

Lumbar puncture may help to determine whether in addition to the thrombosis there is suppurative meningitis. The cerebrospinal fluid is, as a rule, not under increased pressure, and may be sterile ("meningitis sympathica") or contain organisms. In the former case the predominating cells are lymphocytes; in the latter, polynuclears. Its sugar content falls rapidly in infectious cases. The thrombosis may extend from the lateral sinus to the inferior petrosal and cavernous sinus. The latter may be involved on one or both sides.

Occasionally evidences appear of the so-called Gradenigo syndrome, which consists of palsy of the external rectus and symptoms referable to the sensory fifth. These are ascribed either to osteitis or extradural inflammation near the apex of the petrous portion of the temporal bone. Usually the sixth nerve palsy is transitory.

Prognosis.—The prognosis of sinus thrombosis is unfavorable, although benign types have been described in which the thrombus is absorbed or recanalized. This is more apt to occur in primary thrombosis, but recovery from the secondary type has also been reported. In infectious cases the chief dangers are general sepsis and suppurative meningitis. Pyemia seems to develop more readily in thrombosis of the lateral and inferior petrosal sinus than in thrombosis of the superior petrosal and cavernous sinus. When the thrombosis extends from one lateral sinus to the other meningitis is particularly apt to ensue.

In modern times the outlook has been improved somewhat by early operation. A well-developed, diffuse meningitis always makes the prognosis bad. The incidence of localized meningitis or brain abscess is of serious but less grave significance.

Treatment.—In primary thrombosis, treatment is symptomatic and devised to relieve the underlying condition. Stimulants are to be given, the strength of the heart maintained, and nutrition supplied. The headache is relieved by an ice-cap or sedatives. The patient should remain in bed, with the head elevated. In infectious thrombosis exploration with free drainage is necessary. The treatment should also be prophylactic, including careful treatment of the primary disease (infectious lesions of the face, parotid, mastoid) and the evacuation of extradural abscesses. Operative therapy has proved very effective, and may be employed when there are septic thrombosis, gangrene of the wall of the sinus, repeated chills, optic neuritis, and profound constitutional symptoms. Tying off the jugular vein has helped in some cases. The presence of a diffuse suppurative meningitis prevents active treatment of sinus thrombosis, but the demonstration of pus cells or bacteria in the spinal fluid does not preclude operation.

E. D. Friedman.

INTRACRANIAL TUMORS

All expanding lesions within the skull may for clinical purposes be regarded as tumors; it is only rarely possible to diagnose accurately before operation the exact nature of the lesion; on the other hand, it is often easy to name its situation in regard to brain areas.

These conditions are much more common than has been believed. Cushing found, in a General Hospital Surgical Service, 200 brain tumors in 2500 admissions; it is certain that these lesions are often diagnosed as "meningitis," "apoplexy," etc. Even in the autopsy room, centrally situated brain tumors may often be overlooked if not very carefully searched for.

Tubercle in mass formation often attacks the pons, cerebellum, and midbrain of young persons, but lacking calcification of such granulomatous formation capable of obstructing the passage of x-rays, it is difficult to be sure that such a lesion is not gliomatous in character. Gummata of the brain and meninges do not appear in the autopsy room as often as in the textbooks; nevertheless, careful exploration for lues must be made in all cases of suspected brain tumor.

The commonest types of tumor are glioma and neuroglioma; these are rarely discrete and are, consequently, essentially malignant in behavior. Some are highly vascular and into their substance hemorrhages may occur; others may undergo cystic degeneration. The whorl-celled endotheliomata and the fibromata which grow from the acoustic sheath are benign in character. Both are encapsulated and grow very slowly; they are often meningeal in position and so accessible to operation. The slow growth of

the endothelial tumor may produce by irritation of the periosteum of the skull such localized thickening of the bone as to invite the diagnosis of primary osteomata.

Sarcomata are difficult to distinguish by the naked eye from gliomata; they are often metastatic, as from a hypernephroma, and occasionally pigmented as from the uveal tract. Metastases to the brain may occur in both sarcomata and carcinomata; they are usually multiple. Primary sarcoma of the base of the skull is not rare in young persons. It damages, seriatim, the contiguous cranial nerves and is quite inoperable.

Symptoms.—Those due to rise of *general* intracranial pressure: headache, vomiting, and papillo-edema. This triad, in the absence of cardiorenal disease, is presumptive evidence of an expanding intracranial lesion. One or all may be absent. Irritative or paretic phenomena of gradually cumulative character may be so precise that the observer can be sure of the presence of tumor formation before intracranial tension is raised sufficiently to give rise to these general signs. Papillo-edema or choked disk is a mechanical process whereby cerebrospinal fluid is forced from the general pond into the potential space of the vaginal sheath of the optic nerves; it then appears as a swelling at the nerve head, and as it does not involve the nerve-fibers directly, it is compatible for weeks or months with normal vision. Eventually, the albuminous fluid becomes organized, the nerve-fibers are constricted, and consecutive or secondary optic atrophy occurs. Headache is due to stretching of the dura mater, and vomiting, to irritation of the center in the medulla which is pressed into the bony ring of the foramen. The slow vagal pulse is produced in the same manner. Attacks of dizziness are common, due to irritation of the labyrinths or other parts of the cerebellar mechanism, or they may accompany attacks of transient diplopia. Drowsiness, frequent yawning, and a depression of mental acuity are seen in individuals with ventricular distentions; generalized convulsions may occur even though the neoplasm be not placed in either motor area.

Focal Signs.—In some cases of brain tumor focal signs and symptoms never appear; in others, they are equivocal.

Tumors of the Motor Area.—These are usually easy of recognition. The early appearance of focal epilepsy is presumptive evidence of a lesion affecting either the meninges or cortex. A constant site of inception and direction of spread may give precise information as to its position. Transient hemiplegia following a focal fit may gradually become a permanent condition. If the growth be entirely pre-Rolandic there is no objective sensory loss in the contralateral limbs. Should the neoplasm be placed more posteriorly, there may be much paresthesia and loss of the sense of position in even the large joints of the opposite side, in which case astereognosis would be evident in the affected hand. Loss of tactile sense in such conditions is rare and changes in pain and temperature appreciation are unknown.

The progress of all tumors, one must remember, is apt to be slow. Deterioration necessarily precedes destruction of function; inability to finger a violin properly exists before any appreciable loss of power is discovered. It will be found that lesions of the motor zones, if situated on that side of the brain on which the speech faculties are represented, produce defects of speech emission comparable to the losses of fine movement just referred to. Words come sluggishly and are slurred. Inapposite terms are unlikely to

occur, but accurate descriptions are pronounced badly and with difficulty, hesitation, and effort. If the growth be low enough to press on the first left temporal gyrus, inaccuracies of name and description appear rather than difficulty of emission and articulation.

Subcortical growths of the motor areas either do not produce focal epileptic seizures or do so later in the course of the disease. Instead, a progressive hemiplegia occurs; if the tumor be deep enough to infringe on the optic thalamus there may be some alteration of all forms of sensory stimulation on the opposite side of the body, which may also be the seat of deep burning pain produced especially by contact with cold or sharp objects. Athetosis is occasionally present.

Tumors of the frontal lobes are apt to give rise to an inapt purposeless jocosity; occasionally frequent yawning, and urinary incontinence appear early. If the tumor begins in the subfrontal area it may cause pressure on the optic nerve of one side, thereby producing a primary optic atrophy without papillo-edema, though the disk on the opposite side is choked. Vision there is still normal.

Expanding lesions of the occipital lobes are characterized especially by homonymous hemianopic defect in the contralateral visual field. Primarily subcortical growths interfere with optic radiations and produce hemianopia; primarily cortical lesions of the occipital pole, especially of the walls and floor of the calcarine fissure, cause visual fits in the opposite visual field, followed later by loss of function in that field.

These fits consist of crude phenomena lacking constructive quality—twinkling or flashing lights in the affected visual field; one patient said he saw objects in that field "as though through multicolored rain." Alexia or hemianopia may follow visual fits as a transient phenomenon, which may later become permanent.

Tumors of the temporal lobe are difficult to recognize, especially on the right side, owing to the comparative latency of the region affected. Irritation of the uncinate lobules, however, gives rise to paroxysmal crude subjective sensations of taste and smell, and pressure on the neighboring internal capsule may produce a slight hemiplegia of the opposite side of the body; pressure on the optic radiations will possibly result in partial quadrantic homonymous hemianopia. Further, there occur as a result of disturbance of these areas so-called temporosphenoidal fits, which may consist of true dreamy states in which consciousness though retained is oddly transformed, and the relationship between the individual and the external world becomes subjectively altered. Some of these attacks are accompanied by remarkable highly constructed hallucinations, such as "a woman dressed in blue who beckons to me," "an old woman in stinking rags ringing a bell," "figures dressed in eighteenth century costumes," "a lot of negroes." If the growth be on the side of the speech centers there is difficulty in naming seen objects, but no real trouble in speech emission. This condition is perhaps the most characteristic of all the temporosphenoidal speech defects, and is dependent on a degradation of function in the association tracts uniting the visual and auditory centers. These naming errors are instantly perceived by the patient and annoy him. The right word is recognized as soon as it is heard, and so far are these people from being word-deaf that an inaccurate prompting is always rejected.

Tumors of the Centrum Ovale and Basal Ganglia.—If the optic thalamus

be implicated the syndrome peculiar to disease of this organ appears; contralateral athetosis, astereognosis, and depression of the power to appreciate touch on the affected side, explosive sensibility for superficial and deep pain and temperature with subjective burning pain of characteristic nature in the same parts. Motor hemiplegia may be slight. Tumors of one striate body do not usually give rise to postural defects such as occur commonly from epidemic encephalitis.

Tumors of the corpus callosum are characterized by a slow paralysis of all four limbs. Cranial nerve palsies are uncommon. The profound interference with association tracts produces blurring of the mind and interference with speech. Reflexes may not be abnormal; the muscles are waxy and overtoned, so that alternating movements are initiated with difficulty. One patient, under the writer's observation, a police sergeant, first discovered his illness by finding himself unable to relax his grasp of an offender's arm!

Tumors of the quadrigeminal plate almost always originate in the pineal body in young persons. Precocious puberty paints a picture in colors complementary to those used to portray the effects of certain pituitary growths. Cerebral tissue is compressed, but rarely invaded by glandular hypertrophy; the passage from the third to the fourth ventricle may be completely "corked" by neoplasm, and pressure on the oculomotor nuclei gives rise to palsies of conjugate deviation of the eyes, upward and downward movements being first impaired. Slowness of pupil reactions precedes immobility. Nystagmus is almost always present. The gait is ataxic, as are also the movements of the arms. Bilateral pyramidal tract pressure is usual and produces the characteristic paralysis and alteration of reflexes. Severe ventricular distention is the rule.

Tegmental growths usually produce a coarse tremor in the contralateral hand through implication of the rubrospinal tract and the red nucleus. An ipsolateral third-nerve paralysis may occur also. Such tumors are often conglomerate tubercles, most often found in children and adolescents.

Tumors of the pons produce combinations of ipsolateral palsies of the fifth, sixth, and seventh nerves together with paralyses of the opposite limbs. It is important to determine the nuclear origin of these palsies, as abducent lesions often arise from increased general intracranial pressure. In such cases, however, they are not accompanied by ipsolateral facial paralysis nor is the movement of the contralateral internal rectus muscle decreased in amplitude or force. Pontine gliosis may be diffuse and produce the appearance of simple pontine hypertrophy. Papillo-edema appears late. The fillet is extraordinarily resistant to compression, and objective sensory change from this cause is consequently rare.

Tumors of the cerebellum may arise within the brain itself or from the intratentorial meninges or nerve sheaths. Intracerebellar tumors are soft, rapidly expanding, and usually malignant, while those originating outside the cerebellum are usually hard, fibrous, and of tardy growth. Papillo-edema appears early. Dizziness is common.

The sidedness of the growth can usually be determined by the nystagmus, motor ataxia, decreased muscular tone, and weakness. Nystagmus is usually slower and of greater amplitude on looking toward the side of the lesion, and finer and more rapid on looking away from the lesion. The other signs are all more evident on the same side as the tumor. Decomposition

of rhythmical movement may be present in the ipsolateral arm; the finger-nose test may be poorly performed on the same side, and hypermetria may also be seen. The patient stands less well on the ipsolateral than on the contralateral leg. A curious tilted attitude of the head seen in these cases is probably of vestibular rather than purely cerebellar origin.

Tumors growing in the *cerebellopontine angle* more often arise from the sheath of the acoustic nerve; their first symptom is apt to be tinnitus and vertigo followed by progressive nerve-deafness. The fifth nerve is next involved; subjective numbness and tingling in the face and the side of the tongue ensues. By the time the facial nerve is implicated, definite evidence of cerebellar compression is forthcoming. These tumors grow slowly, two to five years may pass before successive involvement of contiguous structures makes plain the diagnosis.

Tumors of the medulla oblongata produce bilateral pyramidal signs and affections of the lowest cranial nerves, which result in difficulties in articulation and swallowing, and arhythmia of the heart and respiration. If the fourth ventricle be invaded, glycosuria is usual and vertigo becomes even more evident.

Tumors of the hypophysis may be recognized both by neighborhood signs and the evidences of altered pituitary function. The former is, most characteristically, bitemporal hemianopia, but almost any form of hemianopic defect may occur. Choked disk is rare and is seen only when the growth has blocked drainage by invading the third ventricle. Primary optic atrophy is usual. An incomplete Fröhlich syndrome—adiposity, eunuchism, and abnormal sugar tolerance—may be an expression of defective pituitary secretion; acromegalic symptoms are less usual.

Treatment.—There is nothing to be said for the expectant treatment of brain tumors.

Action—even though it be but a decompression operation—should follow diagnosis.

In some cases when symptoms are progressive and diagnosis by clinical means impossible, the ventricles may be filled with air and radiographed, as was suggested by Dandy; the ventricular distortion often indicates the site of the growth. Radiotherapy, as yet, has not justified the hopes once placed on it; surgery is still the better instrument. He who cares for patients suffering from brain tumor must bring to his task much thought and stout action. There is need, too, of formidable optimism, for the dice of the gods are loaded!

FOSTER KENNEDY.

ENCEPHALITIS

(Inflammation of the Brain)

Some degree of encephalitis probably exists during any disturbed cerebral activity, whether the disturbance occurs in the realm of consciousness as a whole, or in sleep, movement, sensation, or any of the other physiological processes of the brain. It is difficult in many cases to ascertain whether or not the etiological agents, mechanical or toxic, have actually

destroyed any part of the cerebral circulation, and, in the case of bacterial toxins, whether or not the bacteria are actually present in the brain tissue. With this possibility of error in mind, different types of disease are here discussed.

Two aspects of the disease must be considered, the anatomical and the etiological. Too much reliance on the phenomena indicative of the former may give deficient realization of the potentialities of the latter.

Etiology.—The potential etiological importance of any *infection* to encephalitis deserves mention. In malaria when agglutinated clumps of plasmodia plug the smaller vessels, the brain becomes inflamed as the result of mechanical injury and the degree of damage is proportionate to the extent of the plugging. The ptosis or isolated eye palsy which has followed attacks of whooping-cough might also be attributed to encephalitis produced by the mechanical or toxic manifestations of the infection. The close association of encephalitis with influenza is very striking, and has been frequently written upon for many years. It is possible that many different organisms may precipitate this complication after such a debilitating disease, but epidemic encephalitis should always be kept in mind. It is considered elsewhere. Other infectious diseases which are accompanied or followed by encephalitis are measles, mumps, scarlet fever, chorea, pneumonia, tonsillitis, erysipelas, putrid bronchitis, puerperal and other septicemias, dysentery, typhoid fever, typhus fever, and relapsing fever. The encephalitis may not develop until such infectious diseases have apparently subsided, or even until the patient may have recovered sufficiently to be up and about. Bacteriemic endocarditis may be complicated by a diffuse encephalitis rather than by a more discrete lesion such as embolism. In old arteriosclerotic individuals, debilitated by severe bronchitis, it is fairly common for changes of mentality or disorders of motion or of common or special sensation to develop suddenly. These might be regarded merely as the result of sclerotic processes in the vessels and are hardly to be differentiated from them during life. Postmortem examination, however, sometimes reveals inflammation. Extensively spreading tuberculosis, especially of the miliary type, may cause generalized encephalitis instead of the usual meningitis. Acute anterior poliomyelitis (epidemic infantile paralysis) assumes at times a cerebral form, but patients who recover from it may become quite normal except for such sequelæ as a mild degree of ptosis. Stuporous conditions not otherwise accounted for when poliomyelitis is prevalent should suggest the cerebral form.

Syphilis, apart from the more common cerebral varieties, is not an infrequent cause of encephalitis. The symptoms may be quite unheralded, or may constitute an exacerbation in the course of a more chronic disturbance. Occasionally a syphilitic patient under active treatment becomes more or less stuporous and shows some localizing signs, such as palsy of eye muscles or a speech defect. The cell and globulin content of the spinal fluid may suddenly increase. This condition is possibly due to inadequate treatment or to excessive arsenical medication. The latter type of encephalitis is recognized, only with difficulty, as the result of arsenical poisoning, and the possibility of *cerebral poisoning by other metals*, especially lead, should always be kept in mind. In the more chronic forms of such cerebral intoxication, headache and optic neuritis may be so marked as to suggest cerebral neoplasm.

Carbon monoxid poisoning may cause encephalitis. Its late results (Parkinsonian syndrome) are more likely to suggest the existence of an encephalitic process than are any of the acute manifestations.

Caisson disease may leave disturbances indicative of a condition similar to encephalitis.

During *pregnancy* or shortly after delivery physical and mental symptoms may develop, which at times include phlebitis in the legs, pelvis, or breast. In many such patients there are discrete lesions of the nervous system, which may disappear on natural or artificial termination of pregnancy, or develop into extensive invasions of the brain and spinal cord.

Trauma may result in edema of the brain with great engorgement of the vessels, and multiple microscopical hemorrhages which cause generalized or focal signs similar to those of infective encephalitis.

Fat embolism of the brain, following fracture of a long bone, is characterized by the onset of coma within from eight to forty-eight hours after injury. A suggestive sign often associated with the condition is anuria, due to a similar process in the kidneys. Venous blood, on standing, becomes covered with a conspicuous layer of floating fat.

Encephalitis is more common in the young than in the old, with the exception of an acute form which may occur in the senile, leading to great confusion and unrest.

Symptoms.—The *onset* is usually sudden, though there may have been prodromal symptoms, such as lethargy, headache, and dizziness for several days. At times, however, relatives tell of an altered disposition, unusual lack of industry, a distaste to participate in ordinary recreations, susceptibility to fatigue, and general malaise, which have existed for several weeks. More or less suddenly stupor, indifference, or irritability intervenes. A chill may announce this aggravation and be immediately followed by high fever, although in many cases the temperature scarcely rises to 100° F. A hyperpyrexia of 104° to 106° F. or more may indicate impending death.

In the early stages *stiffness of the neck* may be a prominent sign. The patient even resents attempts to rotate the head from side to side, but in spite of this, lack of Kernig's sign is quite common. All conditions of the *tendon reflexes* are encountered, those of normal character, those usually indicating invasion of the pyramidal tract, and in the more fulminating attacks, their complete loss. Very little information may be obtained from the *cutaneous reflexes* in most cases, unless isolated and intense lesions develop near the motor areas or tracts. *Sensory examinations* are, of course, vitiated by hebetude, irritability, or restlessness. *Convulsions* need only be expected if the process approximates the cortex. If the injury is intense in that region, or in the greater depths of the brain, such a manifestation may be inhibited. On the whole, convulsions are infrequent. More localized disturbances may occur if the lesion be sufficiently discrete—among them monoplegia, hemiplegia, aphasia, hemianopia, eye palsies, nystagmus, deafness, persistence of intolerable vertigo, and ataxia probably of cerebellar origin. There is usually some hyperemia of the fundi oculorum which may develop into well-marked optic neuritis.

The *respiration* may be slowed, hurried, irregular, or of the Cheyne-Stokes variety. The *pulse* is usually rapid, but may be slow. No striking change in the *blood-pressure* is to be expected.

Prognosis.—Many patients undoubtedly recover, and possibly the disease is more common than some physicians might admit. Signs of ill omen are great suddenness of onset; marked severity of signs and symptoms from the beginning; chills; hyperpyrexia; deep coma; and marked restlessness leading to exhaustion. Implication of those parts of the brain-stem which control breathing, swallowing, and the heart action increases the danger of rapid death.

The after-effects may be negligible or to some degree disabling. More or less extensive paralyses may persist. Many conditions commonly diagnosed as epilepsy, even though the habitual convulsive attacks do not occur till late in life, very probably result from the encephalitis associated with infectious disease, particularly if this occurred in early infancy and was characterized by a high fever. Mental changes varying from a state of hypochondriasis and ineptitude for work to a degree of dementia that may be indistinguishable from some of the major psychoses are not uncommon.

Treatment.—One hesitates to speak of treatment with any degree of confidence. Some of the following therapeutic measures are, however, habitually employed: hot foot baths and ice-caps; prolonged warm tub baths (96° to 98° F. if feasible); sponging; hot sheet packs; and free purgation to reduce the mechanical damage to a minimum (1 oz. of magnesium sulphate every hour for six doses for adults or until watery stools result, and proportionately smaller doses for the young). Full doses of pilocarpin have been given when the condition of the patient's strength has not obviously prevented. Improvement may be expected from venesection except when anemia is a complication. Such drugs as salicylates and quinin have their advocates. If salicylates are used, the old rule of a grain per pound of body weight daily, combined with twice that amount of bicarbonate of soda, renders the dose quite tolerable if administered fractionally at short intervals. Large amounts of fruit drinks and other fluids may be given with this, and need not be avoided even if depletion has been attempted by other remedies. A subdued light, quiet, and rest are essential. Rest may be secured in the adult by the administration of chloral hydrate and bromid salts in 5-grain and 10-grain doses, respectively, at one-hour intervals until the desired result is obtained. There need be no hesitation in the free use of these sedatives if they are employed only during periods of great restlessness. The cerebral congestion produced by quantities of morphin sufficient to quiet the agitated patient is thought to render its use undesirable.

In syphilitic cases, if arsenic has not been used within a short time, it is safer to give mercury freely for two or three weeks, and then administer the arsenical preparation cautiously. If, on the contrary, encephalitis has developed during treatment with small doses of arsenic at intervals of one week, marked improvement has followed increase in both the size of the dose and the frequency of administration, even up to a full dose every other day.

As has been suggested above, the encephalitis of pregnancy may be made worse by emptying the uterus. More patients, however, have been seen to improve after this procedure. A repetition of pregnancy seems to carry with it the danger of a recurrence of encephalitis.

Robert G. Armour.

ABSCESS OF THE BRAIN

Etiology.—The conditions which may lead to brain abscess by direct extension are *trauma* of the head or face, *infective conditions* of the ear, eye, or nose and its accessory sinuses, and infections of the face and scalp, such as erysipelas. Metastatic abscess may develop from bacterial endocarditis, particularly of staphylococcic origin, osteomyelitis, bronchiectasis, abscess or gangrene of the lung, pneumonia, rarely pulmonary tuberculosis, empyema, streptothrix infection, actinomycosis, carbuncle, influenza, and other infectious diseases, septic endometritis following abortion, puerperal infection, amebic dysentery, liver abscess, pyonephrosis, and epidemic cerebrospinal meningitis. Metastatic abscesses are likely to be multiple, whereas those due to direct extension are usually solitary.

Septic diseases of the ear are the most common cause of brain abscess, and are responsible for 33 to 50 per cent. of the cases seen in civil practice. Chronic aural diseases cause many more brain abscesses than acute ones. *Otitic disease* may extend into the brain along thrombosed blood-vessels or lymphatics. The infection may travel along the seventh or eighth cranial nerve. Granulations, which develop after operation, may block free outward drainage and force infection into the brain. Sequestra in the temporal bone may be the exciting cause. Extension from the ear may take place through the roof of the tympanic cavity into the temporal lobe of the cerebrum, or from the mastoid cells into the cerebellum. Possibly in a large proportion of cases of aural disease there is some degree of serous, sterile meningitis, but something more than this is required to cause abscess. Even extradural or intradural collections of pus may not lead to abscess.

Trauma of the head, not necessarily fracture of the skull, is the next most frequent cause. Brain abscesses have apparently resulted from injuries which affected neither the skull nor even the scalp seriously, but the condition may be an extension from infected bruises of the scalp. One would expect an abscess resulting from a head injury to be located near the surface of the brain, but this is not always the case, especially if the infection has been carried to some depth by a fragment of bone or a foreign body.

An exacerbation of symptoms or the appearance of new symptoms several days after injury of the head should arouse suspicion of abscess of the brain. After such injury, or in disease of the ear and nose, meningitic symptoms may mask those of brain abscess.

Morbid Anatomy.—An abscess of the brain is a softening which usually contains greenish pus. In chronic abscesses this pus may be sterile or contain organisms of all kinds. Abscesses which develop during exanthemata often contain organisms not usually associated with the primary disease. The lesion may or may not have a well-formed wall. In many instances there is merely a simple gradation from pus to softened brain tissue, edema, and hyperemia; while in others, a somewhat hardened, yellowish wall forms which is perhaps a protection against spread of the disease. Some abscesses rupture into the ventricles of the brain. Evidence of the spontaneous healing of others is thought to be the calcified nodule occasionally discovered after death.

Symptoms.—Brain abscesses may be acute or chronic, that is, the development of the abscess may fairly rapidly produce symptoms which cause death or demand immediate treatment; or run a slow, insidious or

apparently asymptomatic course without evidence of the pathological process until an exacerbation of symptoms or even autopsy reveals its existence. Such chronic abscesses may persist one or two years, or, more rarely, for ten, twenty, or thirty years. Those situated in the depth of the brain tend to remain quiescent longer than those near the surface.

The *general symptoms* of both chronic and acute abscess of the brain are general malaise, loss of weight, poor appetite, constipation, furring of the tongue, and a heavy breath. Chills are not common, but may occur. The patient may not be aware of fever, and the temperature may never, except in the more acute conditions or terminal stages, rise above 100° F. Jaundice may be noticeable in the more chronic cases. When abscesses break into the ventricles, general convulsions, delirium, stupor, tetaniform spasm, chills, hyperexia, rapid pulse, and respiratory disturbances result, to be followed by death with signs of meningitis within a few hours.

In addition to these general symptoms there may be *certain evidences more suggestive of intracranial disease, i. e.*, those associated with increased intracranial pressure (headache, vomiting, and optic neuritis) as well as mental signs suggesting hysteria, neurasthenia, unaccountable change of character, or even a definite psychosis. The most helpful indications of all are those physical signs which not only point with certainty to disease of the brain, but may even indicate clearly the particular area involved.

Of the signs of increased intracranial pressure associated with abscess of the brain *headache* is the most constant. Any constant, or frequently recurring headaches, especially those which prevent sleep, are most suggestive of intracranial hypertension. The location of the headache may vary, or, if fixed, be remote from the seat of the disease. In some cases the skull is tender on percussion. The headache itself is very often of the congestive type, that is, intensified by stooping, coughing, and straining at stool.

The *mental symptoms* of brain abscess are most varied, and it is doubtful if the lesion can be localized with any accuracy by their nature. Hallucinations of formed images have been considered characteristic of disease of the temporal lobe. Delusions, disorders of memory, retardation, and other symptoms suggesting either indefinite or well recognized psychoses may occur. Difficulty of concentration, susceptibility to mental and physical fatigue, moral turpitude, insomnia, restlessness, irritability, drowsiness, and an infinite variety of mental disturbances result from such disease, but, without the physical signs, do not indicate the probable location of the lesion.

Signs.—Physical examination is of the utmost importance since it alone indicates which area of the brain is to be explored. Its nature is suggested by the character of some of the more common signs. *Paralysis* of a part or a whole side may follow involvement of the motor area or its vicinity and of the pyramidal tract in the corona radiata, internal capsule, or crus. It may be of the flaccid type if the abscess has developed rapidly enough or become sufficiently extensive to cause shock, but when only the surrounding areas of congestion and edema implicate these motor areas or tracts, spastic disturbances are more likely to ensue. Furthermore, if the paralysis of a part be incomplete, the abscess is probably not exerting its destructive action at the center representing that part, and careful search should be made for signs of more complete loss of other functions.

This statement, however, must not be too literally accepted in the case of facial paralysis referable to the upper motor neurons, since under these circumstances the lower part of the face is affected much more than the upper part, and the paralysis even of the lower face is frequently inconstant and incomplete. The paralysis may be complete hemiplegia, or be restricted to as small an area as the thumb. The minute lesions are liable to spread, and the more or less rapid involvement of one part after another may be important in differentiating brain abscess from a neoplasm.

Convulsions are suggestive of abscesses at or near the cortex; purulent conditions within the ventricles have been found to cause great *drowsiness* or *coma*.

The *reflexes*, both tendon and cutaneous, demand careful interpretation. Reduction or actual loss of the tendon reflexes and of the cutaneous reflexes, with more or less weakness and hypotonia of the corresponding limbs, suggests a homolateral, cerebellar lesion, but, as has been pointed out above, might be produced by a contralateral lesion of the upper motor neurons. Disturbances of the tendon reflexes may be interpreted as an increase of those of one side above normal (contralateral lesion of the pyramidal tract) or a reduction of those of the other side below normal (ipsolateral cerebellar lesion). In the first instance, some degree of spasticity probably exists in the corresponding limbs, and the plantar, cremasteric, abdominal, and epigastric reflexes may determine diagnosis. In the second instance, hypotonia and ataxia out of proportion to the actual muscular weakness may be the deciding factors.

Homonymous hemianopia may be caused by an abscess in the occipital lobe, but, if accompanied by hemianesthesia, the region of the posterior limb of the internal capsule is involved. If hemiplegia exists, the anterior limb of the capsule is also included.

Aphasia in its different forms may help locate the abscess, but is often misleading, possibly because the popular conception of the speech areas are incorrect, but undoubtedly also because pure types of aphasia are rare. The speech centers are located in the left cortex in right-handed people, and sometimes in the right cortex in left-handed people. *Anomia* is the sign most commonly produced by abscess of the brain, because the purulent processes so frequently occur in the temporal lobe following aural disease. Incomplete *sensory or motor aphasia* may in some cases be confused with the indefinite mental changes and so lose its value as an aid to localization.

Astereognosis may aid diagnosis of abscesses of the parietal lobe, but care must be taken to distinguish this condition from aphasia which prevents description of things the patient recognizes and can name.

Olfactory hallucinations, especially if associated with convulsive attacks or *periodic dream states*, are indicative of a temporosphenoidal lesion. Abscesses of the midbrain, pons, and medulla are rare and almost certainly fatal. *Eye palsies, nystagmus, facial paralysis, difficulty in swallowing, respiratory disturbances* (Cheyne-Stokes respiration), and various *pulse disturbances* may be expected to occur just before death. Implication of the cranial nerves is more often produced by pus in the meninges than by abscess in the brain-stem.

Diagnosis.—Abscess of the brain is often difficult to recognize on account of the frequent absence of signs and symptoms and the possibility of misinterpretation of those which appear.

Choked disk may be absent in a greater proportion of these cases than in those of brain tumor, possibly because the process is largely one of breaking-down tissue rather than of additional growth. For the same reason headache may not be a prominent symptom, and vomiting may occur no more frequently than in mild gastro-intestinal disorders. It is frequently accompanied by nausea. Intracranial disease may not be suspected by those who place too much reliance on projectile vomiting.

The differentiation of brain abscess from *brain tumor* depends on the development of fever and leukocytosis as signs of infection. These symptoms may, however, be absent in the former condition, or be caused by incidental factors during the latter. Chills are most suggestive of abscess, as are also the rapid development and extension of signs and symptoms, but it is to be remembered that *hemorrhage into a glioma* may evoke the same symptoms. The absence or late development of choked disk can be more readily explained by abscess than by tumor.

The symptoms produced by some brain abscesses may be simulated by *uncomplicated otitic disease* and by exacerbations of chronic disease of the ears. The disappearance of such conditions after operation on the ear, or their failure to develop farther if the operation fails to abolish local infection entirely, offers some re-assurance, although continued observation is necessary. *Menière's disease*, occurring in isolated attacks, with complete recovery and absence of physical signs between exacerbations, should not offer difficulty. An *extradural abscess* is not likely to produce localizing signs or those of increased intracranial pressure, but may cause tenderness and edema of the scalp far in excess of that produced by abscess of the brain.

Diffuse, purulent meningitis can be diagnosed with certainty by lumbar puncture. If pus be found in the cerebrospinal fluid in the case of brain abscess, there is also meningitis, and the diagnosis of abscess must depend entirely upon the localizing signs.

The *traumatic and reflex neuroses, hysteria, neurasthenia*, and the *psychoses* may confuse diagnosis at times. The presence of recognized physical signs of organic disease of the nervous system should prevent diagnosis of these conditions unless they can be referred to some pre-existing changes. It is not safe to diagnose these disturbances merely by a process of exclusion, and if there is evidence of a possible abscess of the brain such diagnoses should be made only with the greatest reluctance.

Prognosis.—The prognosis is always serious. Most brain abscesses lead to death.

Treatment.—The only treatment is surgical.

Robert G. Armour.

INTERNAL HYDROCEPHALUS

Definition.—Internal hydrocephalus is a condition characterized by an increased accumulation of fluid within the ventricles of the brain.

History.—Dandy and Blackfan in 1914 published a paper giving pathological and experimental data which established a definite conception of the condition and rendered previous discussions of purely historical value.

Etiology.—An elementary knowledge of the physiological factors governing the formation of the cerebrospinal fluid is essential to the understanding of the pathology of hydrocephalus. In details there are many points where evidence is lacking or where opinions clash, but it is clear that most of the fluid forms in the choroid plexuses within the ventricles and flows through the aqueduct of Sylvius to the fourth ventricle, whence it escapes into the subtentorial subarachnoid space. Part goes down into the spinal canal, part flows upward through channels about the midbrain and reaches the subarachnoid space over the cortex of the cerebrum. It is here that absorption, in large measure, takes place, partly by relatively direct passage through arachnoid villi into the venous sinuses and partly by less obvious paths.

The various lesions producing hydrocephalus do so by interfering with this normal circulation and absorption. Leaving out of consideration the pressure of tumors which cannot be considered here, the block may be the result of congenital anomaly, infection, or injury. The aqueduct may be blocked by *failures of development* which result in obliteration of its lumen. Naturally, such a condition causes distention of the ventricles which cannot be drained by lumbar puncture. When spina bifida exists, hydrocephalus may occur either at birth or after surgical treatment of the spina bifida. The exact relation between the two conditions is not clear, but there is no question that hydrocephalus is one of the most serious dangers involved in surgical relief of the meningocele of spina bifida.

Infections, in fetal life or later, may obliterate the foramina of Majendie and Luschka and prevent the flow of fluid into the subarachnoid space. This causes hydrocephalus, and the fluid cannot be drained by lumbar puncture. Any serious adhesions about the midbrain or extensive obliteration of the subarachnoid space over the hemispheres prevents fluid from reaching the areas where greatest absorption takes place. The ventricles can be easily drained by lumbar puncture, however, and to this type the name of "communicating" hydrocephalus has been given to distinguish it from the "obstructive" or "non-communicating" types.

Injury, particularly the common birth injuries involving tentorial tears, may result in effusion of blood and arachnoid tears about the midbrain. Adhesions may form and prevent entrance of the fluid to the absorbing area. As Beneke pointed out, injury of the vein of Galen may produce back pressure on the choroids. Whether this is a common cause of hydrocephalus is doubtful, but Dandy and Blackfan's work lends support to the theory.

Symptoms.—Advanced hydrocephalus in infancy is unmistakable. The child's head enlarges with a great disproportion between the normal face and the large cranial vault. The sutures spread, the fontanels enlarge and become tense, and the eyes are dislocated downward by pressure upon the thin orbital plates. For a time, even in rapidly progressive cases, the baby may remain bright, maintain its nutrition, and show no evidence of cerebral involvement, but sooner or later, unless the process is arrested, the thin cortex fails to resist the constant pressure, and idiocy, spasticity, and optic atrophy result with eventual death from malnutrition or intercurrent infection. In other instances the condition is arrested before serious damage occurs. In some of these babies the hydrocephalus is so transient that downward dislocation of the eyes and bulging of the fontanel alone suggest the accumulation of fluid.

Obviously the signs are quite different if the increase in fluid takes place after the skull has become rigid. Headache, vomiting, thinning of bone, early optic neuritis or atrophy dominate the syndrome. These late cases, however, are usually the consequence of meningitis or of tumor and cannot be discussed in detail here.

Diagnosis.—The absolute diagnosis of internal hydrocephalus depends on the demonstration of enlarged ventricles. If, on lumbar puncture, almost no fluid can be obtained, it is fair to assume that non-communicating hydrocephalus exists; if, on the other hand, the fluid flows freely and the fontanel becomes soft it is reasonable to conclude that a communicating type is present.

The diagnosis can be made more certain by puncture of the ventricle through the lower angle of the anterior fontanel. The dilated ventricle can be easily tapped and, of course, the thickness of the cortex measured by observing the depths at which fluid is obtained. Dandy's method of ventriculography after injection of air furnishes absolute evidence of internal hydrocephalus. Whether it is a reasonable procedure is a question. The therapeutic resources are so few and the added information gained is so slight that the writer doubts its usefulness. Certainly it is by no means a trivial operation, though before the closure of the sutures the risks are not great. In children with rigid skulls injection of air is a major operation involving serious risk. Injection of dyes into the ventricles with later attempts to recover them from the spinal fluid or the urine furnishes a valuable means of studying the conditions present, but again adds to the risk without giving very definite indications for treatment.

Treatment.—Drugs and endocrine therapy are illogical and of unproved efficiency. The one exception is the indication for mercury and salvarsan in luetic cases. If *syphilis* be present, particularly with involvement of the cerebrospinal system demonstrable by examination of the spinal fluid, active and persistent antiluetic treatment must be instituted. As Jeans has pointed out, this treatment should be as vigorous as that used in adult cases.

Early in the course, particularly after birth injuries or meningitis, *drainage*, either by lumbar or ventricular puncture, may be a life-saving, temporary measure or may aid re-establishment of normal circulation. In these cases puncture should be repeated frequently enough to prevent harmful pressure, until it is clear that the condition is permanent, or until equilibrium between production and absorption is established. One danger must be faced. If spinal puncture does not drain the ventricles, it is obvious that it will do harm because the release of pressure below may favor herniation of the medulla.

Prompt release of cerebral pressure by ventricular puncture is necessary under these conditions.

Surgery is the only hope in progressive hydrocephalus. The problem is largely ethical, for although no operation offers great hope, the alternative is so appalling that well-considered skilfully performed operations are justified if the parents request them. An almost infinite number have been suggested. The fundamental objection to most of them is that the success depends on the establishment and maintenance of a path from the ventricles into the subarachnoid space, and the tendency of the injured arachnoid to form adhesions has, I believe, never been overcome. Dandy has extirpated

the choroid and feels that this severe operation offers hope. It is logical, daring, and perhaps promising. The whole question really comes down, however, to the search for a logical alternative to disastrous inactivity.

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BIRTH INJURIES OF THE CENTRAL NERVOUS SYSTEM

Under the classification of birth injuries is included any condition which may justly be ascribed to damage to the nervous system of a normal fetus as the result of the forces of labor, asphyxia, accident, or hemorrhagic disease within the first few days of life. It should be constantly borne in mind that the occurrence of a birth injury does not necessarily imply that obstetrical care has been incompetent or unwise.

History.—W. J. Little established in 1861 the relation between difficult labor and disorders of the nervous system. At irregular intervals since that time many authors have added important evidence until gradually a clear understanding of the various pathological lesions and their effect upon the development of the child has been built up. It is possible to explain with reasonable accuracy how the forces imposed upon the baby act upon the fetal nervous system.

Incidence.—It is probable that injury of the central nervous system during birth, or immediately thereafter, accounts for more than half of the deaths of viable babies. Furthermore, it is almost certain that such injuries are responsible for the disability of more children suffering from organic diseases of the nervous system than any other single etiological factor except infantile paralysis. The importance of birth injury is further emphasized by the fact that it may cause idiocy and epilepsy which are of great social and economic importance.

Etiology.—In this discussion the fetus during birth can be considered as a central nervous system surrounded by a relatively fragile envelope of flexible bone and connective tissue. During the act of birth this envelope yields to force with consequent distortion. Obviously the central nervous system is affected by pressure, but remains undamaged if the balance between the forces imposed and the resistance of the fetus is not disturbed. The fetus perishes if the vital centers of the medulla and the upper cord are seriously damaged, but it may survive serious destruction of the cord below the vital level or of the brain above the medulla. Usually, although not always, cord injury is the result of the maneuvers incident to breech extraction or to accidents consequent to severe traction on the brachial plexus.

Symptoms.—The character of the symptoms is determined by the extent

and location of the injury. In a general way it can be assumed that injuries high in the cord will cause death by damage to the phrenic nuclei, while subtentorial damage will probably cause death by pressure upon the medulla. For practical purposes, therefore, it is essential to consider the physiological disturbances due to cord injury below the fatal region or to cerebral damage at the midbrain or above.

The intracranial injuries affect two different parts of the brain. If the hemorrhage, as usually happens, is from branches of the vein of Galen, or from that vessel itself, the chief damage will occur in the subcortical regions, notably in the basal ganglia. The consequence will be general disturbance of associated movements, involving rigidity and athetosis. If the circulatory disturbance is severe enough to involve the internal capsules as they pass between the basal ganglia, spasticity will be added to the syndrome.

In more severe cases practically complete decerebration may occur and lead to rigidity and idiocy. In other cases prolonged labor, particularly after the rupture of the amniotic membranes, gives rise to edema and extravasation of blood which is widely scattered within the substance of the brain. Such lesions may easily produce diffuse injury to cortical cells and cause idiocy without conspicuous motor disturbances.

Although our understanding of epilepsy is too slight to allow dogmatic assertions as to its etiology, it is quite clear that among the infinite varieties of damage caused by meningeal or intracerebral injury some may cause attacks.

The fundamental point about the symptoms of cerebral injuries is that the symptoms produced by the injury are exactly analogous to those produced experimentally in animals. The possible variations are infinite. In order to understand them it is essential that the child should be considered from a physiological point of view. It is necessary to get away from a preconceived idea of "spastic paralysis" and from the still more mischievous notion that "cerebral palsy" means mental deficiency, and to find out, by rather simple physiological reasoning, what the undamaged residue is. Upon this residue, rather than upon what is gone, depends rational prognosis and treatment.

Diagnosis.—To determine whether any particular neurological lesion dating from early infancy is due to birth injury, faulty development, or infection is frequently impossible. Certain syndromes, however, such as Mongolian idiocy, congenital hydrocephalus, microcephalus, or spina bifida, can be clearly distinguished; and likewise the various familial degenerative diseases such as Werdnig-Hoffmann progressive atrophy, pseudohypertrophic muscular dystrophy, Friedreich's ataxia, etc.

There remains, however, a great group of non-progressive conditions which may be considered from two points of view. From the first, the physician may attribute to birth injury only those conditions with conclusive history. He will then be forced to rely on vague conceptions of heredity, fetal infections, and faults of development, conceptions which, although safe from an argumentative standpoint, lead nowhere in particular. The second point of view depends on the pathological evidence that the central nervous system of babies dying at birth or shortly thereafter shows evidence of vascular injury in at least 50 per cent. and probably in about 65 per cent. of all cases. Such evidence leads to the conviction that a baby of apparently normal development at birth who presents evidence of neurological

disturbance is handicapped by the results of the forces used in bringing him into the world. Such a view is unquestionably difficult to establish, but it presents points of value. Prophylaxis may be rendered possible by certain revisions of obstetrical technic, the horror of "tainted heredity" or other menacing phrases is eliminated, and the way is prepared to study the physiological possibilities of a central nervous system damaged by sudden accident.

The essential points in diagnosis are to differentiate the fixed, non-progressive type of disturbance from the progressive type and to bear in mind that tumors occur in babies.

Treatment may for convenience be divided into measures for the immediate relief of injury and the later efforts to minimize the existing physiological disturbances.

The recognition of cerebral pressure is the most important single point in caring for the injured baby after birth. Munro and Eustis advocate early lumbar puncture with manometric observations on the cerebrospinal pressure, followed in many cases by repeated drainage if the pressure remains high. This relatively simple procedure supplemented by ventricular puncture and by transfusion, where there is adequate evidence of decreased coagulation, constitute the immediate therapeutic measures. Decompression is a serious operation and, on the whole, is falling into deserved disrepute.

Later on, operative intervention to attack the intracranial or intraspinal lesion is extremely unsatisfactory. Most surgeons, after considerable experience, have abandoned such operations or perform them only as desperate measures.

The effort of the physician should be centered upon the attempt to make use of every bit of intact nervous tissue and to avoid hopeless therapy. Idiocy, severe convulsions, and total transection of the spinal cord cannot, in all probability, be relieved by treatment. On the other hand, practically every child with less than these maximal disabilities is worth working over.

Education, patiently and hopefully carried on, restores certain patients to efficiency. Orthopedic procedures of infinite variety may help, but it cannot be too persistently repeated that the successful education of the child handicapped by birth injury is of primary importance, and that this education cannot be properly directed unless a clear survey of the physiological assets is made at the beginning of treatment.

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Diseases of the Peripheral Nerves

NEURITIS

(*Inflammation of the Nerves*)

Neuritis is an inflammation of the nerves. It may involve a single nerve, when the condition is known as a mononeuritis or localized neuritis, or a large number of nerves, when it is known as a multiple neuritis or polyneuritis.

Mononeuritis (*Localized Neuritis*).—Although the disease may be limited to a single nerve trunk, as in traumatic neuritis, several nerves may often be involved. The condition is then termed mononeuritis multiplex.

Etiology.—Localized neuritis may result from trauma, chronic intoxication, infection, extension of inflammation, and chilling. Not only direct *injury* of the nerve, but also the contusion, traction, and compression resulting from forced muscular movements, the tearing and stretching caused by dislocation or fracture, the reduction of dislocations, and the traction of the head or arms of the infant during labor may evoke mononeuritis. Other etiological factors are compression by callus, exostoses, cervical ribs, tumors, hypertrophic osteo-arthritis, and repeated severe compression by crutches or industrial instruments, accidental hypodermic introduction of chemicals (arsphenamin, sera, ether, alcohol, etc.). *Chronic intoxication* by alcohol or metallic poisons frequently renders a nerve so sensitive that a subsequent slight injury may produce neuritis. During and after *infectious diseases* (typhoid fever, smallpox, diphtheria, tuberculosis) neuritis may develop in its localized as well as in its multiple form. *Extension of inflammation* from adjacent parts (caries, bone syphilis, and, more rarely, diseases of joints) also causes the disturbance. *Cold* is an etiological factor which has been overemphasized, although it is a common precursor of peripheral facial palsy.

Morbid Anatomy.—Inflammation of nerves may originate in and be practically limited to the perineurium (perineuritis), be situated mainly in the interstitial tissue (interstitial neuritis), or within the nerve-fibers (parenchymatous neuritis). In the first two conditions the nerve is swollen, infiltrated, and red. An exudation of migrating leukocytes is found in the fibrous framework of the nerve. The nerve-fibers may not be involved, but there is usually an increase of the nuclei of the sheath of Schwann. The myelin is fragmented and the axis-cylinders at times become varicose or undergo granular degeneration. Finally, the nerve-fibers may be completely destroyed and replaced by fibrous connective tissue.

Parenchymatous, or degenerative neuritis, produces a lesion similar to the Wallerian or secondary degeneration which occurs in the peripheral end of a severed nerve. It first affects the medullary sheath, then the axis-cylinder, and last the neurilemma. The myelin becomes turbid, and splits into fragments, small globules, and granules. The axis-cylinder likewise becomes subdivided, swollen, and liquefied. Extravasated leukocytes engulf the disintegrated products and become granule or scavenger cells. The neurilemma and its nuclei frequently remain intact. The nerve shrinks in volume and appears grayish, grayish-red, or translucent, and may finally appear as a fibrous cord. The inflammation is sometimes limited to a portion of the nerve or to several isolated areas of inflammation.

Occasionally the whole trunk may be affected. Thus a focal, a disseminated, and a diffuse neuritis are described.

The opinion of older writers about the frequency with which ascending neuritis is associated with septic wounds (neuritis migrans) has not been generally sustained. A descending neuritis in which the infection is continued into the muscular tissue (neuritis fascians or Eichorst's neuritis) has been described.

Symptoms.—The symptoms may be divided into two groups, loss of function of the nerve and irritative phenomena of the inflammation. The first group when present differ only in degree, the second are variable and inconstant. In conditions due to trauma the loss of function produces flaccid paralysis with atrophy and reaction of degeneration in the affected muscles, sensory loss, and at times trophic disturbances. Unless the median or internal popliteal nerves are affected, pain is not a constant, severe, or prominent symptom. Various paresthesias, crawling, slight burning, and formication may be present. When the median or internal popliteal nerves are affected an exceedingly painful type of neuritis (causalgia) may appear. This is characterized by severe, diffuse, burning pain, which is increased by movement, sudden noise, or other startling occurrences. It is partially relieved by continuous application of moist dressings. So severe is the pain and so urgent the need for moisture that wounded soldiers under fire have often been known to apply rags saturated in urine to the sensitive areas.

The consistency of the symptoms due to injury leads to the conclusion that many manifestations of the conditions due to other causes are the result of pathological changes outside the nerve. In disturbances due to sepsis, arthritis, and infectious diseases pain is a prominent symptom. It is dull, aching, boring, at times continuous, at times throbbing, and often complicated by sharp, lancinating, lightning-like flashes. Nocturnal exacerbations are common. All movements which tend to stretch the affected nerve increase the pain; it is also aggravated by coughing, sneezing, and straining. Frequently the pain is increased by distortion of the inflamed parts about the nerve, as by an arthritic joint for example. The inflamed nerve may be swollen on palpation and is frequently tender to pressure. The skin may be reddened, glossy, dry, or moist and clammy, the subcutaneous tissue edematous, and the nutrition of the nails defective.

Prognosis.—The extent of injury and the character of the underlying lesions determine prognosis. Minor degrees of trauma produce only temporary disability if the cause can be removed. Accidental introduction of chemicals may produce irrecoverable lesions. The neuritis produced by adjacent osteo-arthritis can usually be cured, whereas that consequent to caries cannot.

Treatment.—Neuritis due to trauma may produce a permanent physiological interruption in the nerve, and can be treated only by such surgical procedures as resection and suture. Conditions which follow compression are likewise treated surgically by removal of the cause and, in addition, by neurolysis. Causalgia may finally require injection of 60 per cent. alcohol into the nerve. In other types of neuritis the underlying cause (arthritis, etc.) must be treated. Proper splinting, to prevent overstretching of paralyzed muscles and contractures, should be applied. The general treatment is the same as that for multiple neuritis.

Multiple neuritis, polyneuritis, or peripheral neuritis is an acute or subacute, disseminated inflammation or degeneration of symmetrically distributed nerves, which affects principally their distal portions.

Incidence.—It is a comparatively uncommon disease, although rarely a wide-spread epidemic may occur, like that which resulted from arsenical poisoning among beer drinkers in England, and from lead poisoning among children in Australia. The two sexes are equally affected. Multiple neuritis is most frequent in the second, third, and fourth decades of life. Non-diphtheritic polyneuritis in children is rare. Thomas and Greenbaum, who reviewed the literature in 1907, found 138 cases and added 8. The aged are sometimes affected with senile or atheromatous polyneuritis.

Etiology.—The causes may be grouped as toxic, infectious, and unknown. Among the most common *exogenous toxins* are alcohol, lead, arsenic, coal-tar products, carbon monoxid, nitrobenzol, mercury, copper, zinc, phosphorus, silver, and emetin. The *endogenous toxins* develop during diabetes, the cachexia of tuberculosis and syphilis, and beriberi. The *infectious diseases* which most often play an etiological rôle are diphtheria, influenza, typhoid fever, measles, scarlet fever, whooping-cough, puerperal fever, septicemia, parotitis, gonorrhea, and syphilis. Acute infective polyneuritis, acute febrile polyneuritis, and infective neuronitis may also be causes. There are in addition various unknown factors.

Morbid Anatomy.—It is now generally admitted that multiple neuritis is not confined to the peripheral nerves. The nerve lesion is only part of a general intoxication which affects the spinal cord and the brain. One of the types described by Osler, acute febrile polyneuritis, is now identified with a similar disease called acute infective polyneuritis or infective neuronitis. This produces wide-spread changes in the posterior root ganglia, spinal roots, ventral horn-cells, and Betz cells of the cortex. The condition differs from acute infectious multiple neuritis (acute pernicious multiple neuritis, Heine-Medin disease), which is allied to poliomyelitis, occurs during epidemics of this disease, and usually proves fatal within a few days or weeks.

The alcoholic paralysis, undoubtedly due to polyneuritis, may be associated with slight central changes in the spinal cord. The central changes in diphtheritic paralysis are even more marked. Lead sometimes affects the spinal cord and frequently the brain. Arsenic more rarely affects the spinal cord. So-called diabetic neuritis has been shown by Kraus to be in many cases a disease of the posterior roots and posterior columns of the spinal cord.

Symptoms.—Whatever the cause, the general symptoms of multiple neuritis are similar, and vary only because of the characteristics of the particular intoxication or infection. The disease often begins with prodromata which sometimes persist for weeks. The patient complains of numbness, slight fever, tingling in the extremities, and sensations of heat and cold; weakness then follows either suddenly or subacutely. At times the paralysis is accompanied by fever. Convulsions may occur, particularly in children. Some pain develops and the weakness increases. The muscles and nerves become very tender, while the skin may be reddened or slightly edematous. After a few days the patient may be unable to stand. Complete paralysis of the anterior tibial muscles and of the extensors of the wrists may ensue after a week or two.

The *paralysis* is flaccid and is followed by atrophy and other trophic changes. The response to electrical stimulation varies from an early loss of reaction to faradism to the complete reaction of degeneration. The paralysis is usually symmetrical. Certain groups of muscles (the extensors) are more susceptible than others. One of the characteristic features is the association of *sensory changes* with the paralysis. Tactile anesthesia, often associated with hyperalgesia, may be an early symptom. Later, the temperature and pain sense is diminished and retarded. The sensory loss is either patchy or diffuse. The frequent loss of deep sensibility produces a pseudotabetic or ataxic form of the disease (diabetes, diphtheria).

The *deep reflexes* are usually diminished or absent and the superficial reflexes disappear. As a rule, the distal portions of the extremities are the first to be affected. In rare instances the motor cranial nerves may show the first signs of the disease. The bladder may occasionally be affected for a short time. Other visceral reflexes are not disturbed.

Special characteristics of certain forms of multiple neuritis are noteworthy. *Alcoholic polyneuritis* most often affects women. The extensors are the muscles usually involved; this produces foot-drop and wrist-drop. The sensory symptoms are variable. The course is, as a rule, favorable. Mental symptoms are striking; delirium is common; and hallucinatory states, delusional states, and delirium tremens may occur. In other cases Korsakoff's syndrome, characterized by disorientation, loss of memory for recent events, and fabrication, appears. *Arsenical polyneuritis* resembles alcoholic neuritis and is distinguished by the general symptoms of intoxication, gastro-intestinal disturbances, puffiness of the lids, dermatitis, hyperkeratosis, changes in the nails, jaundice, and other evidence of hepatic disease. Muscular tenderness is especially common, and often leads to severe contractures of the toes and fingers. Poisoning may follow administration of medicinal drugs, contamination of food and drink, or accidental ingestion of vermin-destroying mixtures. *Lead neuritis* is often associated with the general signs and symptoms of lead poisoning, a "lead line" in the gum margins, secondary anemia, stippling of erythrocytes, and abdominal pain and constipation. The neuritis is frequently confined to the upper extremities. Sensory changes rarely are present. Intoxication results from the handling of lead products (paints, type, lead pipe), the smelting of ores, the contamination of water, and the use of cosmetics. *Diphtheritic paralysis* is frequently associated with dysphagia, regurgitation of fluids, and nasal speech. Paralysis of the ocular accommodation reflex is very common. When the polyneuritic symptoms occur in the extremities they are often associated with ataxia. This may at times be present without paralysis.

Rarely, recurrent polyneuritis has been described.

The course of the disease varies with the intensity of the underlying lesions. As a rule, the symptoms increase during the first four to six weeks and then diminish. While the disease is progressing the sensory symptoms are particularly prominent. The paralysis disappears later than the disturbances of sensation. At times contractures develop as the result of the paralyses.

Diagnosis is not difficult. The disease is differentiated from *tabes dorsalis* by the acute onset, the absence of Argyll Robertson pupils and bladder disturbances, and the presence of paralysis. Serological examination of the spinal fluid is pathognomonic in tabes. Multiple neuritis is

differentiated from *anterior poliomyelitis* by the massive paralysis; in the latter disease this gradually recedes; in the former, the motor disability gradually increases. The absence of sensory changes and the asymmetrical distribution of paralysis, as well as the very late changes in reaction to electrical stimulation in anterior poliomyelitis, are further means of differentiation. There is a remote similarity between mutliple neuritis and progressive muscular atrophy, the dystrophies, periarteritis nodosa, polymyositis, acrodynia, and hysteria.

Treatment.—The first step in the treatment of multiple neuritis is to remove the cause. Elimination of some of the metallic poisons may be favored by administration of potassium iodid, catharsis, and sulphur baths. Sodium thiosulphate may be given for arsenical polyneuritis.

In the endogenous types of polyneuritis Oppenheim used diaphoresis. If the patient's strength permits, the secretion of sweat may be stimulated by hot baths; otherwise, by hot packs or hot-air applications, and hot drinks and aspirin. A strengthening diet is necessary in all forms of neuritis.

The *pain* may be relieved by warm fomentation or antineuralgic drugs. General tonic medication may be prescribed—cod-liver oil, iron, quinin, and strychnin. During the first stages of the disease absolute rest in bed is imperative. Proper splints must be applied to prevent contractures and overstretching of the paralyzed muscles. When the condition has become stationary, or shows the first signs of improvement, physiotherapy, consisting of massage, passive movements, gradually increasing resistive exercises, and electrotherapy, is necessary. Subcutaneous injection of strychnin is useful in persistent paralysis. Residual paralysis and contractures must be treated surgically.

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NEUROMATA

Nearly a century ago Odier recognized that tumors may grow from nerves. Neuromata have been classified according to Virchow as true and false. *True neuromata* are tumors arising from or composed of actual nervous tissue. They are exceedingly rare and are found practically only in connection with the sympathetic system. They are benign and vary in size from that of a pea to that of a child's head. They may be relatively soft or very hard. Multiple, true neuromata have been observed chiefly

in children. They have been distributed in the peripheral part of the body under the skin. They are very numerous; in Bruns' case 160 were counted. The patients otherwise are quite well.

The *false neuromata* are tumors which originate in the perineurium, epineurium, or endoneurium. They may be neurofibroma, neurosarcoma, neuromyxoma, etc. Although they develop on all of the nerves, the spinal is that chiefly affected. Their etiology is obscure. Usually they develop in the first half of life, and in many instances have been hereditary. In multiple false neuromata (general neurofibromatosis) large numbers of tumors form on many or all of the peripheral nerves. R. W. Smith has reported a case in which 450 were counted on one extremity and 2000 were present on the body. All types—plexiform neuromata, pachydermatocele, or neuromata elephantiasis and multiple neuromata, neurofibromata, or molluscum fibrosum (von Recklinghausen's disease), as well as tubercula dolorosa—are expressions of the same abnormal tendency. These lesions may be associated with pigmentation of the skin in the form of freckles, blotches, or diffuse areas.

The most prominent *symptom* is pain, which radiates from the tumor to the periphery of the nerve. It is usually intermittent, but may become continuous and agonizing. Paresthesia is occasionally observed, weakness is rare, and the deep reflexes are seldom affected.

The only available *treatment* is excision, although Ludwig Kenez reported that the hypodermic administration of fibrolysin produced successful results.

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THE CEREBRAL NERVES: PERIPHERAL AND CENTRAL DISTURBANCES IN FUNCTION

I. The Olfactory Apparatus

Before any conclusions can be drawn about the acuity of smell, careful local examination of the nasal fossæ is necessary. Thereafter, the essential oils (lemon, wintergreen, peppermint, and clove) may be employed to test the sense of smell first in one nostril and then in the other.

Hyposmia and Anosmia.—Organic.—Organic hyposmia or anosmia is the result of various conditions. The sense of smell may be diminished or completely lost when the free endings or the nerve-cells of the olfactory epithelium are injured by chronic coryza associated with the growth of nasal polypi; by influenza, or by diphtheria; by lesions of the fifth nerve which cause trophic changes in the mucous membrane; or by caries of the underlying supporting osseous tissue (ethmoidal sinusitis). Pressure on the olfactory neurones at any point between their origin in the nasal mucous

membrane and their incorporation in the hemispheres interferes with the conduction of olfactory stimuli. Meningeal thickening, neoplasms which arise in the floor of the anterior cranial fossa or in the frontal lobes and press on one or both olfactory tracts, abscesses, hemorrhages, areas of softening near the olfactory pathways, or any general increase in intracranial pressure may reduce or destroy the sense of smell. Laceration of one or both tracts caused by fracture of the floor of the anterior cranial fossa may produce unilateral or bilateral hyposmia or anosmia.

Functional.—Partial anosmia is frequently found in individuals who constantly handle wine or cognac; in extreme, confirmed smokers; in those who habitually take cocain by inhalation or snuffing; and in the aged and infirm. Anosmia is also associated with hysterical disturbances of the other senses; this type may be unilateral and usually involves the side in which the other senses are abnormal.

Hyperosmia.—Increased acuity of smell is a variable and indefinite condition which is usually a symptom of hysteria.

Parosmia, a perversion of the sense of smell, may be a symptom of generalized cerebral disease, or may follow focal disturbances of the function of the olfactory lobe. Such perversions are usually of an unpleasant character. They occur in the aura of epilepsy with sufficient frequency to justify a special classification (hippocampal epilepsy) of that disease, and are also common in the insane.

Neoplasms arising in the uncus produce a definite syndrome characterized by extreme olfactory hallucination—usually unpleasant, rarely pleasant—and by generalized convulsive seizures or localized tremors and twitchings which have been ascribed to pressure on the red nucleus. There is frequently also a homolateral exophthalmos with marked venous engorgement due to pressure on the cavernous sinus, and occasionally the oculomotor nerves which lie in the wall of the sinus are involved. Pressure on the brain-stem may, in addition, evoke other signs of involvement of the central nervous system, as well as the general manifestations of increased intracranial pressure.

II. The Visual Apparatus

Strictly speaking, the peripheral portion of the optic apparatus is an intrinsic part of the brain and not in any way analogous to the cerebrospinal nerves. The only parts of the optic apparatus homologous to these are the layer of receptors in the retinæ and the central processes which arise from these receptive cells. The remainder of the apparatus is formed by an evagination from the primitive vesicular neural tube.

Extraneural Factors in Visual Defects.—Disturbances in the sense of vision of extraneural origin may result from lesions in the various media of the eye. These defects must be eliminated by the proper methods.

Retinal Factors in Visual Defects.—*Retinitis* may be a disease of the retina itself or the expression of some systemic or degenerative neural disease which particularly affects the retina and produces wide-spread visual disturbances.

Primary Retinitis.—In primary or simple retinitis the evidence of inflammation is limited to swelling, distention of the blood-vessels, and occasional hemorrhages. This condition is considered by some authorities to be the first stage of the more advanced forms, but by others it is thought

to be a definite type without demonstrable cause. Overuse of the eyes, uncorrected errors of refraction, poor illumination, exposure to cold or to excessive light may be the etiological factors.

Retinitis pigmentosa may appear as a definite and specific disease *sui generis*, which is not associated with syphilis. It is usually hereditary and is often found in the offspring of consanguinous parents. It is frequently accompanied by other congenital defects such as deafness and poor intelligence, and sometimes by cataract and other visual anomalies. The condition appears in early life and becomes progressively more marked. In the early stages it is manifested by night blindness (*nyctalopia*) and by concentric contraction of the fields of vision. The progressive diminution of vision rarely produces complete blindness.

Secondary Retinitis.—(*a*) *Retinitis Secondary to Renal Disease.*—According to Gowers, there are three fairly well differentiated types of retinal change in nephritis: one more or less *degenerative*, in which wide-spread evidences of degeneration appear throughout the retina without any change in the disk; another of *hemorrhagic* character, in which there is only slight evidence of inflammation; and a third, the *inflammatory type*, in which the marked retinal change is associated with a great deal of edema and changes in the disk suggestive of increased intracranial pressure. In the first type, the toxic character of the metabolic disturbance is paramount and the retinal elements suffer almost direct selective destruction. In the second, the hemorrhagic lesions may be flame-shaped and extend over a considerable part of the retina, or linear and remain closely confined to the region of the blood-vessels. These lesions are usually associated with evidence of marked arteriosclerosis in the fundus. In the third, the papilloedema, which may produce 4 to 5 diopters of swelling, renders the appearance of the disk exactly similar to that associated with intracranial neoplasms.

Although retinal changes occur in the course of both acute and chronic nephritis, they are more commonly associated with interstitial nephritis. In all conditions suspected of having a renal basis the eye-grounds should be carefully examined, as there is often no apparent relationship between the extent of renal involvement and the manifestations in the fundus. Retinitis may also appear as a symptom of the general toxemia of pregnancy. This type usually tends to clear up after delivery.

(*b*) *Retinitis Secondary to Syphilis.*—The retinitis secondary to syphilis has been described as occurring in acquired syphilis, but it is more usually associated with the inherited type. The primary inflammation seems to be in the choroid, while that in the retina is a secondary manifestation which results in extensive accumulation of black and brownish pigment between the retinal elements, and in a considerable thinning of the retina and the choroid. This thinning materially increases the translucency of the retina so that the choroidal vessels are easily seen through it. The accumulations of pigment are extensive.

(*c*) *Retinitis Secondary to Hemal Disturbances.*—The retinal changes associated with anemia, malaria, leukemia, and some general diseases, such as diabetes, purpura, chronic lead poisoning, etc., are probably due largely to alterations in the constituents of the blood. In both *primary* and *secondary anemia*, *leukemia*, and such *generalized diseases* as diabetes and purpura there is a marked tendency to hemorrhage throughout the body.

Such hemorrhages in the retina are frequently followed by thickenings which result in scarring and thus disturb the function of the visual elements.

(*d*) *Retinitis Secondary to Degeneration of the Central Nervous System.*—*Amaurotic family idiocy,* which begins in infancy, is manifested by progressive loss of sight which results in complete blindness, and by increasing idiocy. The disease is usually limited to Russian or Polish Jews. In the early stages the macular region is found to be definitely pale and atrophic; as the condition progresses a cherry-red spot appears in its center. This lesion is associated with wide-spread degeneration of the entire nervous system which finally causes early death.

The *second type* of amaurotic family idiocy which attacks *adolescents* is much less severe and does not always lead to complete blindness and loss of intelligence.

In both types of the disease not only the visual fibers but also the light fibers of the retina are affected and the reaction of the pupils to light, accommodation, and convergence is disturbed. Localized non-homonymous losses of vision (scotomata) result from local destruction of the visual elements. They are appreciated by the patient as dark spots in the field of vision.

Neural Factors in Visual Defects.—Neural causes of visual defects are of two types: those which interfere with the visual pathway, and those which disturb the cortical perceptive system. Lesions in the visual pathway may be considered according to the manifestations found in involvement of the several anatomical divisions of the pathway. In considering the defects of vision which result from local lesions, it is essential to remember the anatomical arrangement of the fibers which constitute the various parts of the visual pathway from the eyeball to the cortical centers. In differential diagnosis the fact that the optic nerve and tract contain both light and sight fibers is of importance. Both types of fibers remain commingled as far caudad as the primary visual centers. There the sight fibers combine to form the optic radiation (radiation of Gratiolet), while the light fibers pass to the superior colliculus and form a part of the reflex arc which controls the retinal illumination. It is this arrangement which renders possible the pupillary reactions of Wernicke. A lesion between the optic chiasma and the primary visual end-stations produces blindness in the temporal half of the homolateral eye and in the nasal half of the contralateral eye. This homonymous hemianopsia is associated with loss of pupillary reflex reaction to a beam of light confined strictly to the abnormal temporal or nasal field, since the lesion involves both the light and sight fibers. If, however, the cause of the disturbance be in the centrum semiovale or in the occipital lobe, an homonymous hemianopsia will result, while the light reflex of the blind area persists, since the light fibers have separated from the sight fibers peripheral to the lesion. These reactions are very difficult to demonstrate.

Local Disturbances of the Sense of Vision.—*Lesions of the Optic Nerve.*—The optic nerve may be rendered abnormal by laceration or by compression or injury caused by inflammation within the orbit, in the optic foramen, or between the optic foramen and the optic chiasma. *Laceration* usually results from fracture of the base of the skull which involves the walls of the orbit, the anterior cranial fossa, or the most anterior portions of the middle cranial fossa. Neoplasms, which arise in the orbital cavity, from the contents of the orbit, or in the periosteum or bone of the wall of the

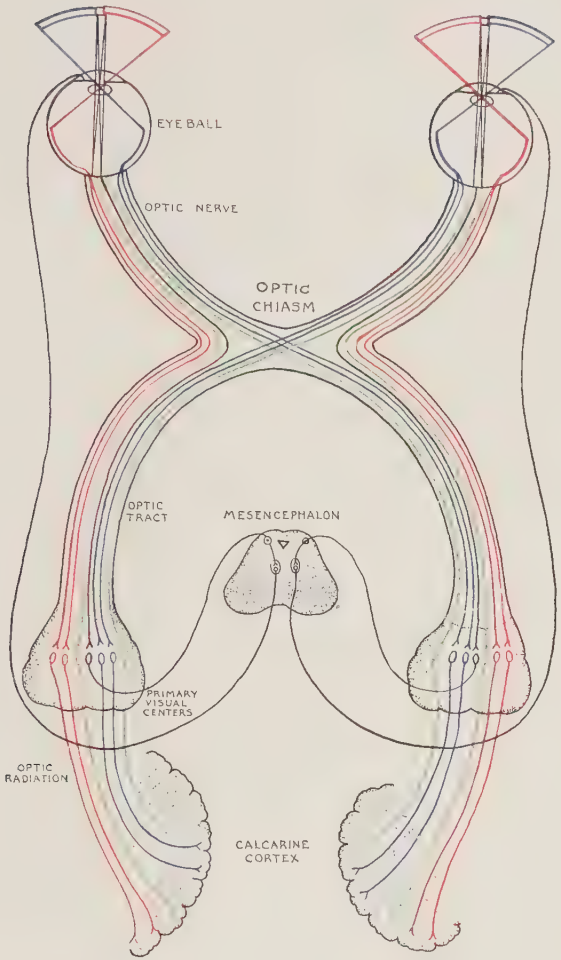

Fig. 29.—The visual pathway. This diagram indicates the reversal of the visual and retinal fields, the course of the fibers which arise from the various portions of the retina, and the path of the light reflex: Red indicates the temporal fibers. Blue indicates the nasal fibers. Green indicates the macular fibers. Black indicates the light fibers. The uncrossed course of the temporal fibers, the crossed course of the nasal fibers, and the partially crossed and partially uncrossed course of the macular fibers is indicated. The primary visual centers, consisting of the pulvinar of the thalmus and the lateral geniculate body, are indicated together with the course of the optic radiation to the calcarine cortex. The switching of the light reflex stimulus from the primary visual centers to the tectum of the midbrain and its connection with the efferent oculomotor neuron governing the sphincter iridis is also shown.

orbit or optic foramen, may *compress* the optic nerve. Tumors which arise in the caudal portions of the orbital gyrus of the frontal lobe may, by impinging directly on one or both optic nerves, destroy or diminish vision. If the pressure be exerted on only one nerve, there is usually evidence of primary atrophy in the fundus of that eye and development of a central scotoma, while papillo-edema appears in the other eye. *Optic atrophy* may result from primary tumors of the optic nerve (gliomata), tumors of the nerve-sheath (neurofibromata and sarcomata), and from involvement by metastatic neoplasms. *Compression* of the optic nerves is also produced by acute or chronic inflammation in the walls of the optic foramen. Periostitis or osteitis is usually caused by chronic infections such as syphilis and tuberculosis. *Osteitis deformans* and *leontiasis ossia* may cause sufficient hypertrophy of the bone around the optic foramen to compress the optic nerve and thus produce partial or complete loss of function.

Inflammation of the contents of the orbit, either hematogenous or by direct extension from the eyelid or accessory nasal sinuses, may produce optic neuritis which results in diminution or complete loss of vision in one eye. This begins as a central scotoma because the more susceptible central macular bundle first suffers injury.

A very frequent cause of involvement of the optic nerve is infection of the ethmoidal cells which, by direct extension along the periosteum, may cause an inflammation, first in the central fasciculi and finally in the entire nerve.

Lesions of the optic chiasma may be associated with disease of the hypophysis, hypencephalon, bony tissues of the sella turcica, or of the blood-vessels or the meninges in its vicinity. The *inflammatory processes* which may affect the chiasma are usually direct extensions from an inflammation within the sphenoidal sinus or from localized meningitis. Lesions which affect the central portions of the chiasma involve the fibers which cross from the nasal half of each retina to the contralateral calcarine cortex. This results in a loss of visual capacity in the nasal halves of the retina of both eyes (bitemporal hemianopsia). The lesion which most often produces this syndrome is an hypophyseal neoplasm. In many instances this may affect one side more than the other and even involve one entire optic nerve; it then produces complete amaurosis in the eye on that side and temporal hemianopsia in the other. A rather more unusual type of involvement of the chiasma is a bilateral aneurysm or varicose dilatation of the carotid arteries which may press upon the chiasma from one or both sides. Lesions of the internal carotid artery which press on the side of the chiasma interrupt the uncrossed fibers from the temporal half of each retina and produce a *binasal hemianopsia.*

Lesions of the Optic Tract.—The etiology of lesions of the optic tract is similar to that of the conditions already described, namely, neoplasms which arise from the base of the skull or from the meninges; localized meningitic processes, or intracerebral neoplasms which press on the optic tract in its course to the primary visual end-stations, the lateral geniculate body, and the pulvinar of the thalamus. Such involvement produces contralateral homonymous hemianopsia with corresponding loss of the light reflex.

Lesions of the Primary Visual End-stations.—The primary visual end-stations in the thalamus and metathalamus consist of the lateral geniculate body and the pulvinar of the thalamus. Lesions in the vicinity of these structures are usually due to vascular disease, embolism, thrombosis, hemor-

rhage, or neoplasms. These produce contralateral homonymous hemianopsia, usually accompanied by such other disturbances in cerebral function as partial or complete contralateral hemianesthesia or hemiplegia. The vertical gaze may also be paralyzed by a disturbance in the subthalamic aberrant pyramidal bundles which supplies the nuclei of the third nerve. From the primary end-stations the visual pathway leads through the retrolenticular portion of the internal capsule and the centrum semiovale of the hemisphere to the calcarine cortex.

The optic radiation in the occipital lobe of the hemisphere may be destroyed by neoplasms arising from the brain tissue itself, the meninges overlying the brain, or the osseous tissue of the skull; by vascular disease (hemorrhage, embolism, or thrombosis) of one of the large vessels supplying the cerebral substances; and by diffuse or local infection (encephalitides, brain abscess). This results in an homonymous hemianopsia with the pupillary phenomena of Wernicke, which may be associated with a contralateral hemianesthesia or hemiplegia. Lesions in the temporal lobe which affect only a portion of the optic tract may produce sector deformities in the visual fields.

Lesions of the Calcarine Cortex.—Lesions of the entire cuneus produce contralateral homonymous hemianopsia. Bilateral disease of the cunei causes complete blindness. This may arise from either neoplastic or vascular cortical disease that is bilaterally symmetrical, from pressure by new growths of the falx as it lies between the two occipital lobes, or from trauma. The usual cause of such lesions is neoplastic, infectious, or vascular disease of the occipital lobe.

Transient hemianopsia, usually of the homonymous type, is not uncommon in the more severe types of migraine. It may be associated with the scintillating scotomata which are often found in this disease. These disturbances probably depend upon transient anomalies of circulation.

Pathological processes which result from meningeal or osseous disease (chronic inflammation or neoplasms) affecting the lateral or the ventral surface of the occipital lobe disturb the psychic appreciation of vision, although the primary qualities, the perception of form, color, etc., still remain intact. This condition is called *"mind blindness."* The higher psychical elaboration of the primary visual constituents is lost, and although the patient is still able to see, he cannot appreciate the meaning and significance of objects. He is no longer able to recognize objects as such, and there is no understanding of their uses. The meaning of written and printed words is entirely lost.

General Causes of Disturbance of Visual Function.—The general causes of disturbance of visual function are exogenous toxins, endogenous toxins, and degenerative conditions associated with disease of the central nervous system.

Exogenous Toxins.—The excessive use of tobacco may produce gradual, progressive diminution of the central fields of vision. This is first evidenced by inability to recognize red and green (a central scotoma for red and green). If the intemperate use of tobacco continues, a complete optic atrophy with total loss of sight (unilateral or bilateral) results in very rare cases. Similar involvement of the optic nerve follows poisoning by the heavy metals, particularly lead, and by methyl alcohol, and also by quinin in individuals who are hypersensitive to this drug. *Hemeralopia*

(day blindness), in which the patient sees better in a dim light, is not uncommon in these exogenous amblyopias.

Endogenous Toxins.—Diminution of vision is sometimes associated with severe or repeated infection of the respiratory tract, as well as with syphilis, tuberculosis, typhoid fever, erysipelas, influenza, pneumonia, tonsilitis, malaria, beriberi, the toxemia of pregnancy, and extensive cutaneous burns.

Results of Both Endogenous and Exogenous Intoxication.—The result of endogenous and exogenous intoxication is optic neuritis of three types: axial, interstitial peripheral, and diffuse. *Axial neuritis* (neuritis of the papillomacular bundle) affects the optic nerve between the eyeball and the optic chiasma. It may be acute or chronic. The acute type appears in young adults, particularly in females. It is usually manifested by a sudden cloudiness or diminution of vision, with frontal headache and orbital pain which is increased by pressure on or movement of the eyeballs. The loss of sight is rapid and usually soon reaches its maximum. With the loss of sight the headache diminishes. Usually no changes can be seen by ophthalmoscopic examination. The pupil of the affected eye is larger than the other, and, as a rule, contracts on direct stimulation, but quickly dilates despite continued stimulation. After the acute stage there is gradual recovery of sight at the periphery, although varying degrees of central scotoma persist. Final loss of vision may be unilateral or bilateral, may affect only color, or may be limited to central or paracentral scotomata.

The chronic form is more common. It is the type usually associated with chronic alcoholism and nicotin poisoning. The condition often begins with a red-green scotoma. In the earliest stages it may be recognized by the difference between the appearance of red and green in the peripheral and central fields of vision. Acuity of vision gradually diminishes. The fundus may be entirely normal or may appear hyperemic or mildly neuritic, with some temporal pallor. The prognosis depends on the etiology of the syndrome. The characteristic lesion is degeneration of the papillomacular bundle. This may, in severe cases, become complete unilateral or bilateral optic atrophy. An hereditary form of axial neuritis is described which seems to affect males, and is transmitted by unaffected females (Von Leber's atrophy). It progresses acutely or subacutely, one eye or the other being in advance. It is evidenced by a central scotoma which affects color vision before perception of form, and gradually increases in size. Nyctalopia, the reverse of hemeralopia, is a common symptom. Total blindness results in about 33 per cent. of cases. The fundus usually shows optic atrophy, which is most marked in the temporal half of the disk. This disease is very rare.

Interstitial peripheral neuritis, in contrast to axial neuritis, involves the periphery of the optic nerve before the centrally placed papillomacular bundle and concentrically limits the fields of vision for white instead of producing a central scotoma for colors. Central vision usually remains sharp, even for color. Ophthalmoscopic examination reveals simple or neuritic atrophy. Very occasionally the evidences of papillo-edema appear. This condition usually follows systemic infections, such as measles, diphtheria, influenza, metallic poisoning (lead and arsenic), typhoid fever, diabetes, the meningitides, disease of the nasal sinuses, and particularly syphilis.

Diffuse neuritis, which involves the entire optic nerve, causes marked amblyopia or blindness. It is often associated with acute myelitis and develops in the course of infectious diseases, particularly influenza and syphilis, and in conjunction with scarlet fever, malaria, yellow fever, and erysipelas. Diffuse optic neuritis may also accompany epidemic encephalitis. It may become so severe that a papillo-edema of 4 or 5 diopters of swelling results. This is indistinguishable from the optic neuritis with papillo-edema which is evoked by increased intracranial pressure. The cause of this encephalitic papillo-edema is usually thought to be a leptomeningitis which occludes the foramina of exit of the cerebrospinal fluid, and thus produces internal hydrocephalus.

Associated Degenerative Conditions of the Central Nervous System.—*Optic neuritis* or *optic atrophy* may appear in the course of multiple sclerosis. It is a very common evidence of this disease and is usually confined to the temporal halves of the disks, which are markedly pale. In association with tabes and general paresis it often appears also.

Myasthenia gravis may produce disturbances—usually more or less transient, concentric constriction—of the visual fields. This may progress during the active course of the attack and then regress as the other symptoms of the disease disappear. More often, however, myasthenia gravis produces transient diplopia with inconstant correlation of images.

Postneuritic secondary or inflammatory optic atrophy usually follows papillitis or neuritis, retinitis or pigmentary degeneration of the retina, embolism of the central artery or glaucoma; or trauma. The disk has a dense white or grayish color with more or less irregularity and obscuration of the margins. The minute vessels disappear completely, and the lamina cribrosa is hidden by the organized exudate. The retinal arteries are narrow and show a white line and the veins are enlarged and tortuous. After injury to the nerve, atrophy may not appear for several weeks, although vision is immediately diminished or lost. A surprising amount of vision may remain after optic neuritis or optic atrophy. In differentiating between a papillitis and a papillo-edema the degree of retention of vision may be of some aid; it is always much greater in the latter than in the former condition, although the lesions may appear almost identical.

Hysterical amblyopia may be unilateral or bilateral. The narrowing of the visual fields increases characteristically during examination. The extent of the visual fields varies greatly from time to time and the color fields may be inverted.

Papillo-edema is usually consequent on an increase of the intracranial pressure by intracranial neoplasms or internal hydrocephalus. Intracranial neoplasms may arise from the cerebral tissue itself, from the meninges, or from the osseous tissue of the skull. The presence of these in addition to the normal intracranial contents increases the pressure within the skull and presses the tissue fluid out into the various tissue spaces. The perineural sheaths of the optic nerves participate in this general distention and, consequently, typical papillo-edema develops. In the early stages there is usually only an increase in the diameter of the veins. As the pressure continues to increase, however, the veins become tortuous and the margins of the disks, indistinct. Radial lines appear which extend from the center of the papilla over the edge of the disk into the retina, and the retina itself begins to participate in the edema. This increases and the

papillæ become raised above the level of the surrounding retina. There is consequent obliteration of the normal physiological cup, the vessels pass across the disk, and then dip over the edge, to reappear as they traverse the retina. The focus of the retina and the top of the disk then vary, and different lenses must be introduced into the ophthalmoscope to permit measurement of the degree of swelling at the top of the disk. Hemorrhages and patches of localized exudate become evident at this stage, scattered throughout the retina. If the cause for the increased intracranial pressure be removed, recession may take place with organization of the patches of exudate and the hemorrhages. The edge of the disk never, as a rule, returns completely to normal, but remains blurred because new connective tissue has formed after the organization of the inflammatory tissues. The end-result of a papillitis may be a return to normal, optic atrophy with the retention of a considerable degree of visual acuity with concentric contraction of the visual fields, or blindness from the postneuritic atrophy. It may also be associated with echinococcus cysts, cysticercus cellularis, brain abscess, lues, tuberculosis, hydrocephalus, sinus thrombosis, nephritis, lead encephalopathy, leukemia, epidemic encephalitis, multiple sclerosis, and pachymeningitis hæmorrhagica.

Chromatopsia is the ability to recognize colors. *Achromatopsia* or color blindness may appear as an hereditary or acquired defect in vision. In the hereditary form it may occur as a loss of the ability to distinguish red and green, the individual being able to recognize the blue-yellow combinations (partial achromatopsia), or it may extend to all colors (complete achromatopsia). It usually affects both eyes. *Acquired achromatopsia* may follow extensive disease of the retina or of the optic nerve. Visual perversions may appear without apparent changes in the retina. The most frequent is red vision (erythopsia) which appears after extraction of a cataract. No satisfactory explanation of these visual disorders has been found.

The excessive use of santonin as a vermifuge may disturb the color vision. The first bluish discoloration is later replaced by yellowish discoloration (*xanthopsia*) which renders blue objects greenish and violet objects indistinct.

III. The Oculomotor Apparatus (Third, Fourth, and Sixth Nerves)

Lesions of the Oculomotor Nuclei and the Efferent Fibers of the Oculomotor Nerves.—Nuclear lesions of the oculomotor nerves result from the acute encephalitides associated with such acute infectious diseases as measles, scarlet fever, chickenpox, smallpox, influenza, etc., with acute epidemic encephalitis and polio-encephalitis, and with such chronic inflammatory or degenerative diseases as chronic anterior poliomyelitis, chronic nuclear encephalitis, progressive nuclear degeneration, Landry's paralysis, amyotrophic lateral sclerosis, multiple sclerosis, syringomyelia, tabes, botulism, and syphilis. The hemorrhagic polio-encephalitis of Wernicke, a rapidly developing disease which produces a nuclear affection of the oculomotor apparatus, but usually spares the internal muscles of the eye, may cause paralysis. It is characterized by headache, vertigo, vomiting, and progressive involvement of the oculomotor nerves. A much less well-defined group of diseases, which may include paralytic vertigo, exophthalmic goiter, pseudoparalytic myasthenia, myasthenia gravis, and ophthalmoplegic migraine, may evoke oculomotor palsies of various types.

Disturbances of the oculomotor apparatus are frequent in severe *migraine* (so-called ophthalmoplegic migraine), which, after the acute attack, result in paresis or paralysis of one of the oculomotor mechanisms. This condition is analogous to weakness sometimes found in one or both extremities of one side or the other after convulsive attacks.

The nuclei may also be involved in hemorrhagic vascular disease, thrombosis, or embolism of the small vessels which enter the posterior perforated space to reach the oculomotor and trochlear nerves, or the larger trunks supplying the pons and cerebellum to reach the abducens nucleus. Usually with these vascular disturbances the pyramidal tract is involved, so that two types of hemiplegia result, superior and middle alternating. In the former, the homolateral oculomotor nerve and the contralateral upper and lower extremities are involved; in the latter, the homolateral abducens nerve and the contralateral upper and lower extremities are affected.

The oculomotor nuclei may be exposed to the pressure exerted by neoplasms arising in the vicinity of either the collicular plate, the pineal gland, the tegmentum of the mesencephalon, the caudal portion of the thalamus or the interpeduncular region, while the abducens nucleus receives pressure from neoplasms arising in the pons, the cerebellopontile angle, the cerebellum, and the structures which form the boundaries and contents of the fourth ventricle. These nuclei may also be affected by hydrocephalus due to disease in the region of the roof of the fourth ventricle with dilatation of the third ventricle, the Sylvian aqueduct, and the fourth ventricle.

The nerves themselves may be involved in their passage through the meningeal envelopes of the brain in certain infectious processes, such as acute and chronic meningitis, and often in association with suppuration in and about the middle ear. They may also be affected by the neuritis accompanying acute infectious diseases, especially diphtheria and acute rheumatic fever, by pneumonia and diabetes, and by poisoning with nicotin, lead, alcohol, and other exogenous and endogenous poisons. Trauma, especially that due to fracture of the base of the skull across the cephalic portion of the posterior cranial fossa or through the middle cranial fossa, may also injure the nerves in the cavernous sinuses. Injury in this vicinity is usually coincident with interference with the cutaneous innervation of the ophthalmic division of the trigeminal nerve because this nerve is also present in the wall of the cavernous sinus.

In their extra-axial course the nerves may be singly or collectively affected by neoplasms arising in the base of the skull, the pons or midbrain and the cerebellopontile angle, the meninges, the hypophysis, the floor of the hypencephalon, the uncus or other neighboring parts of the temporal lobe, or in their own sheaths (Von Recklinghausen's disease). They may also be involved by aneurysmal dilatation of the vessels of the circle of Willis.

Disease of the bones of the skull (osteitis deformans, leontiasis ossia, and acute or chronic infection of the bone or periosteum) may constrict the sphenoidal fissure sufficiently to interfere markedly with the functions of the third, fourth, and sixth nerves. Tumors and infections in the orbit may destroy peripheral conduction in the oculomotor nerve-fibers.

Paralysis of the motor nerves of the eyes results in limitation of movement of the eyes, divergent or convergent strabismus, secondary deviations,

and diplopia. The *limitation of movement* is the direct result of the paralysis, while the *strabismus* (divergence in the axes of the two eyes) is produced by the unopposed action of the unparalyzed, anatomically antagonistic muscles. The *secondary deviations* are caused by overaction of the sound eye during efforts to innervate the abnormal eye. The *diplopia* results from retinal displacement due to the strabismus, which allows the image to fall on an unaccustomed point on the retina. This leads to false judgment of the relative position of objects. The identity of these false images can be immediately recognized when colored lenses are used. Since the equilibrium of the body is largely controlled by ocular movements, the erroneous projections and disturbed harmonies caused by oculomotor dysfunction produce vertigo (ocular vertigo). The object seen by the sound eye is, of course, the true image; that seen by the paralyzed or affected eye is called the false image.

Disease of the ciliary ganglion may give rise to internal ophthalmoplegia (paralysis of the sphincter iridis and of the ciliary muscle). The Argyll Robertson pupil is never associated with this condition, since the reaction to light, accommodation, and convergence is lost. One type is never destroyed while another is preserved.

Involvement of either the *nucleus of the third nerve* or the efferent nerve evokes complete loss of the movements of the pupil in response to light and convergence, and also a complete loss of the power to vary the curvature of the lens for near and distant vision. This is termed a complete internal ophthalmoplegia. The eyeball is turned outward by the unopposed action of the superior oblique and external rectus muscles; and the eye rests fixed in the outer canthus in a position of external strabismus. The upper eyelid droops so that in some cases it completely covers the eyeball; this so-called ptosis is due to failure of innervation of the levator palpebræ superioris.

A lesion of the *nucleus of the fourth nerve* or of the efferent nerve alone is relatively rare and difficult to demonstrate. Theoretically, however, the trochlear nerve, through the superior oblique muscle, should turn the eyeball downward and outward, so that paralysis of this muscle would turn the eyeball somewhat upward, inward, and out of line with the other. The patient is often made aware of this condition by seeing double on going down stairs.

A lesion of the *nucleus of the sixth nerve* or its efferent nerve in the axial or extra-axial course produces internal strabismus by paralyzing the external rectus muscle which opposes the internal rectus of the eye (innervated by the oculomotor nerve). The result of this internal strabismus is diplopia (double vision). The displacement of the affected eye is opposite to the direction of traction of the paralyzed muscle.

In ocular palsies the head may be held in definite, habitual positions in an attempt to compensate by the position of the head for the lost action of the paralyzed muscle.

A lesion of the nucleus of the *sixth nerve* produces a somewhat more extensive disturbance of the ocular movements than does involvement of the abducens nerve itself, because fibers from the abducens nucleus enter the *posterior longitudinal fasciculus* and are distributed to the nuclear segment of the oculomotor nucleus which controls the internal rectus of the opposite eye. The connection permits the carefully co-ordinated and

synergized movements of the external rectus of one eye and the internal rectus of the other in lateral gaze. Lesions of the nucleus of the sixth nerve itself interfere with the movements of the internal rectus of the opposite eye, whereas involvement of the peripheral course of the abducens nerve alone does not. Consequently, nuclear lesions of the sixth nerve cause paralysis of the conjugated movements of the two eyes toward the side of the lesion, although there is still independent action of the internal rectus of the opposite eye.

Isolated palsy of any of these three nerves also disturbs the fibers which carry deep sensibility from the ocular muscle-fibers. Such conditions are apt to produce a sensation of dizziness and unsteadiness because the normal stream of afferent impulses which arises in the ocular muscles and reaches the central nervous system is interrupted. Total bilateral external ophthalmoplegia may apparently be due also to congenital malformation or very early encephalitis. The function of the internal musculature remains normal.

Oculomotor movement may also be disturbed by *myositic* infiltration in any of the muscles of the eye. This occurs relatively more often in the external rectus than in the others. It may produce transient paralysis or paresis of the affected muscle.

The Pupil.—The *outline* of the pupil may change for many reasons. The pupils are normally equal in size, round and regular in outline, and central in position. They may, however, be congenitally unequal; usually, unless affected by disease of some kind or another, their outline is regular despite the difference in diameter. Inequality in the size of the pupils is called *anisocoria*. The *size* of the pupil normally varies a great deal because it is controlled by general physiological factors, psychic and emotional processes, trains of thought, conditions of local control, etc. *Irregularities* of the pupils may be due to old inflammation or injury followed by the formation of synechiæ between the iris and the lens, to operation, or to congenital malformation.

The normal pupillary unrest results from interaction of the constrictor and the dilator fibers of the pupil. Loss of this activity is evidence of a pathological disturbance within the oculomotor mechanism. If the interaction becomes excessive, it is described as *hippus* (excessive alternation between contraction and dilatation). This may be one of the earliest signs of organic abnormality in this reflex neural pathway, and is common in the early stage of tabes and general paralysis. Similar disturbances in the pupil also develop in chronic alcoholism and syringobulbia.

Under certain conditions there may be a *paradoxical pupillary reaction* (dilatation of the pupil instead of contraction on stimulation by light). This is not at all uncommon in tabes and is an example of the interacting synergy always present in all reflexes which involve synergic, antagonistic elements.

Mydriasis, or dilatation of the pupil, may result from paralysis of the sphincter pupillæ or from stimulation of the dilator pupillæ. Dilatation most frequently follows destructive processes which involve the central nuclei and the intra-axial and peripheral pathways connected with the oculomotor nucleus, the oculomotor nerve, and the ciliary ganglion. Irritative pupillary dilatation is less easily demonstrable. The pupil usually dilates as sight diminishes or is lost as the result of primary or secondary

disease of the optic nerve. Mydriasis is, of course, very common in most forms of syphilis of the central nervous system because almost pathognomonically the oculomotor nucleus and its associated mechanisms are involved.

Myosis is excessive contraction of the pupil. It may be due to stimulation of the sphincter pupillæ or to paralysis of the dilator pupillæ. It is a normal result of forced efforts to close the eyelids and is normal during sleep. The spinal myosis of tabes follows paralysis of the dilators of the pupil. This is the most usual cause for the myosis associated with disease of the central nervous system. The condition also occurs in cerebral arteriosclerosis and alcoholism.

The Pupillary Reflexes.—*Direct Light Reflex.*—Normally, the iris responds by contraction of its circular fibers to introduction of light into the cavity of the eye. The extent of the contraction of the sphincter iridis depends on the amount of light which enters the eyeball; excessive illumination reduces the pupil to a pinpoint. The action of the sphincter is, of course, balanced and synergized with the radially arranged fibers of the dilator pupillæ. This muscle is supplied by a branch from the ciliary ganglion derived from the vegetative nervous system. Stimulation of the involuntary nervous system dilates the pupil. It is only through delicate co-ordination of the sphincter and the dilator muscle that the normal pupillary reaction is obtained.

The *consensual light reflex* is the reaction of the right pupil to stimulation of the left retina by a ray of light, and *vice versa*. It is brought about through the superior collicular commissure which transfers impulses received by one retina to the colliculus of the other side, whence they pass to the sphincter pupillæ of the unilluminated eye.

A pupil which has lost the light reflex, but retained the reflex of accommodation and convergence, is known as the *Argyll Robertson pupil*. In this condition the pupil is moderately constricted. The Argyll Robertson pupil is almost pathognomonic of syphilis of the central nervous system, and appears characteristically in tabes, and somewhat less often in general paralysis. It is also associated with chronic alcoholism, less commonly with sclerosis of the central nervous system, and may accompany lesions of the temporal lobe, particularly tumors.

The Ciliospinal Reflex.—The pupil also dilates reflexly if the skin of the neck be scratched or pinched on the same side. The center for this reflex is in the eighth cervical and first thoracic segments, and it innervates two involuntary muscles: Muller's muscle, which aids in raising the upper lid; and Horner's muscle, which holds the eyeball forward in the orbit. Involvement of this ciliospinal center evokes symptoms of irritation: the pupil enlarges; the eyeball becomes somewhat more prominent than that of the opposite side; and the palpebral fissure is larger than in the normal eye. If the lesion becomes paralytic, the manifestations are reversed: the pupil constricts; the eyeball sinks into the orbit; and enophthalmos and a sympathetic ptosis appear. Disturbance of the ciliospinal reflex may be one of the earliest signs of tabes. *Horner's syndrome* (exophthalmos, myosis, and sympathetic ptosis) also accompanies disease of the lower portion of the medullary tegmentum, where the oculopupillary center, which controls the ciliospinal center in the eighth cervical and first thoracic segments, is located.

The *reflexes of accommodation and convergence*, essentially similar in character, are elicited by the approach to the eyes of an object and by alternately looking at a distant and a near object. The eyes converge and the pupils constrict. In the reflex of accommodation each eye may be tested independently. The pupil contracts as the gaze is transferred from a distant to a near object. The reflex cuts off the peripheral rays which tend to render indistinct the outline of near objects. It is essentially a visual reflex and probably involves the occipital cortex in its arc. Loss of accommodation with retention of the light reflex (the converse of the Argyll Robertson pupil) is not uncommon after diphtheria, and is usually accompanied by other manifestations of postdiphtheritic neuritis.

Disturbances in the Internuclear Communications.—Oculomotor disturbances produced by involvement of the *posterior longitudinal fasciculus* appear either as dissociation of the conjugated movements of the two eyes or as abnormal movements (skew deviation) of the eyes.

Inflammation, degeneration, vascular accidents, and destructive neoplastic involvement of the posterior longitudinal fasciculus dissociate the conjugated lateral movements of the eyes by interrupting the fibers which link the nucleus of the abducens nerve of one side with the internal rectus segment of the oculomotor nucleus of the other side.

Other abnormalities of the posterior longitudinal fasciculus arising from the vestibular complex and from the cerebellar, synergic control of the ocular muscles may appear as *nystagmus*. This is an oscillatory movement of the eyes which is of three types: vestibular, cerebellar, and congenital. In *vestibular nystagmus* the movements of the eyes are divided into a slow phase and a rapid phase. The slow phase is a slow drifting away of the eyes from the point of fixation because of vestibular influence, while the rapid phase is the voluntary return of the eyes to the point of fixation. This type of nystagmus is most easily seen in extreme lateral gaze, but may sometimes be demonstrated in vertical gaze (vertical nystagmus). Rotary nystagmus is due to impaired activity of the oblique muscles. *Cerebellar nystagmus*, which usually accompanies all movements of the eyeballs or fixation of the eyes, is a true asynergia of the ocular muscles which results in unbalanced activity of the muscular apparatus due to disturbed cerebellar control. In *congenital nystagmus* the eye movements are in wild disorder, quite extensive, irregular, and follow no definite pattern.

The nystagmus due to imbalance of the ocular muscles is most commonly seen in multiple sclerosis, but also develops in myasthenia gravis, Friedreich's ataxia, alcoholism, individuals with congenital mental defects, and in miners who must work in a poor light with their heads in abnormal positions. It may be produced by mechanical irritation of the semicircular canals, rotation and stimulation by electricity, or by the injection of cold or hot water into the external auditory meatus.

Disturbances in Conjugated Movements.—Supranuclear disease of the oculomotor pathways causes disturbances of the conjugated movements of the two eyes. If the lesion be irritative in character, a conjugated movement of the eyes away from the side of the abnormal stimulation results. The individual looks away from the side of the lesion. If, however, the lesion be paralytic or destructive in character the eyes turn toward the abnormal side.

Lesions of the aberrant pyramidal system, which passes to the oculo-

motor nucleus, destroy the conjugated movements of vertical gaze. Paralysis of vertical gaze is often associated with disease of the colliculi or of the pineal gland, which produces direct pressure on the oculomotor nuclei. It may be caused by nuclear paralysis, but is usually an expression of more wide-spread disease. Paralysis of conjugate movements has been said to occur in *exophthalmic goiter* as a symptom which is probably dependent on the general toxemia. In this condition, the exophthalmos may be so extreme as to produce a complete external ophthalmoplegia, without influencing the reactions of the pupils to light and accommodation.

Hysterical ptosis may simulate disease of the third nerve, except that on passive elevation of the lid there is no evidence of association of other ocular palsies as there would be if the disturbance were organic. Hysterical ptosis is also usually accompanied by other hysterical stigmata. In hysteria any attempt to raise the lid with the finger evokes resistance, which is never present in paralytic ptosis.

Exophthalmos is usually found in exophthalmic goiter in which it is accompanied by other physical signs within the orbit: the sign of von Graeffe, *i. e.*, slow and imperfect following of the movements of the eyeball by the eyelid; the sign of Stellwag, a widening of the palpebral fissure; and the sign of Moebius, a weakness of the power of convergence. Exophthalmos also accompanies pronounced myopia. It may be seen in acute myelitis, and is frequently found unilaterally in association with arteriovenous aneurysm of the cavernous sinus, and with disease of the soft parts or the bony tissue which forms the orbit. If the exophthalmos be the result of systemic disease it is usually bilateral; if it result from local abnormalities, it is usually unilateral. It may be so marked as to interfere with proper closure of the eye (lagophthalmos). This may cause keratitis with serious consequences.

Enophthalmos is due to disease of the sympathetic or the preganglionic fibers which originate in the ciliospinal centers, and may also follow disease within the orbit or loss of the orbital tissue. It is almost always unilateral.

IV. The Trigeminal Nerve

It has for a long time been a question of debate whether the sense of taste belongs to the trigeminal or to the facial nerve, but the greater weight of evidence now seems to demonstrate that it is an essential function of the seventh cerebral nerve. The distribution of the taste fibers is merely taken over by the trigeminal nerve. A discussion of abnormal taste is, therefore, included in the consideration of the seventh cerebral nerve.

Diminution in Sensibility of the Trigeminal Nerve (*Hypesthesia or Anesthesia*).—The trigeminal nerve supplies sensation to the skin of the face, the anterior half of the scalp, the mucous membrane of the lips, mouth, tongue, and pharynx, the accessory sinuses of the mouth and nose, the teeth, and portions of the dura mater, as well as, in conjunction with the ciliary ganglia of the vegetative system, to the cornea and conjunctiva of the eye. Disturbances in sensation may be partial (hypesthesia) or complete (anesthesia). If complete, they may include all types of sensibility or be merely a dissociation of sensation, so that certain types are affected while others remain uninvolved. The disturbance may also be either peripheral in type and correspond to the distribution of the three branches of the Gasserian ganglion (the ophthalmic, maxillary, and mandib-

ular divisions) or segmental and limited to areas which correspond to the circumoral arrangement of the trigeminal dermatomes described by Déjerine. Careful plotting of the area of disturbed sensation indicates the peripheral or segmental character of the sensory loss.

Peripheral Disturbances.—Disturbance in the peripheral distribution of the branches of the Gasserian ganglion is manifested as a reduction in superficial sensibility (touch, pain, and temperature), which may be partial or complete according to the severity of the lesion. It results from infectious processes in the skin and mucous membranes, the bones of the skull, and the foramina of entrance in the base of the skull; from meningitic processes within the cranial cavity; and from neoplasms arising from the cranial bones either external to the skull, within the foramina or from the base of the skull, from the dural envelopes, and from the pons or cerebellum, which produce pressure upon the afferent portions of the nerve sufficient to interfere with the transmission of sensory stimuli by the nerve. Neoplasms may also originate in the nerve itself or in the nerve-sheath (Von Recklinghausen's disease) and produce hypesthesia or anesthesia of any division or of the entire nerve, according to the site of pressure.

The divisions of the nerve may also suffer laceration following direct penetrating wounds, or when a fracture of the base of the skull passes through the foramina or tears the dura implicating the nerve trunks. The ophthalmic division, on account of its location, is also exposed to damage by aneurysm of the internal carotid artery, arteriovenous aneurysm, or thrombosis of the cavernous sinus, and by neoplasms which arise in the temporal lobe or hypophysis.

Segmental Disturbances.—Disturbances in sensation which appear according to the segmental distribution of the trigeminal nerve are much less common than those of the peripheral type. They depend upon intra-axial disease, and may result from such vascular lesions as hemorrhage, thrombosis, or embolism, from neoplasms in the medulla oblongata and the pons varolii, and from degenerative conditions such as syringobulbia, multiple sclerosis, and epidemic encephalitis. In these types of disease if the lesion progress from below upward, the disturbances will first affect the most aboral segments and gradually extend to the more circumoral dermatomes.

Dissociative Disturbances.—Pathological processes within the neuraxis, particularly syringobulbia, may dissociate the various types of sensibility associated with the fifth nerve. Lesions which particularly affect the descending root of the fifth nerve seem to attack the pain and temperature fibers especially, whereas lesions in the caput of the nucleus of the trigeminal nerve affect the more discriminative types of sensibility. It is possible also to involve the secondary pathways of the fibers which go to the spinal or medullary fillets: the former carry pain and temperature sensations, the latter the discriminative types. This produces the sensory dissociations which may be so easily demonstrated in various types of spinal disease.

Central Disturbances.—Vascular disease or neoplasms in the cerebral hemispheres, so located as to interfere with the fiber pathways or the terminal nerve-cells, may also disturb sensation in the face. Limitation of such disturbance to the face alone is very rare.

The ability to recognize stimulated points in the distribution of the trigeminal nerve, to distinguish the distances between two simultaneously

stimulated points, and part of the ability to recognize the character of objects touching the surface may survive complete loss of superficial trigeminal sensibility. These deep types of sensation have been ascribed to other nerves, particularly to the seventh cerebral nerve. The course by which these stimuli reach the neuraxis is still unknown.

Trophic Disturbances.—Trophic changes in the mucous membrane supplied by the trigeminal nerve may disturb the sense of smell and also the sense of taste. Trophic disturbances in the eyeball are of extreme importance where pathological lesions or operative interference with the ophthalmic division or the Gasserian ganglion is concerned. Trophic ulceration of the cornea and of the conjunctiva may produce permanent opacity and disturbance of vision. Such trophic lesions favor the spreading of infection with resulting ophthalmia. Interference with the glandular affector fibers of the fifth nerve may materially reduce and change the salivary and lacrimal secretions.

Involvement of the cells of the Gasserian ganglion by some unknown infection may evoke *herpes zoster* in the distribution of any of the three divisions of the nerve. This is characterized by burning and itching, followed shortly by the development of groups of small vesicles on a reddened base, which in time ulcerate. It is usually associated with marked discomfort, pain, and tingling, which is often followed by actual hypesthesia.

Increased Sensibility (*Hyperesthesia*).—Pain in the distribution of the trigeminal nerve may result from irritative lesions of the nerve trunks, inflammation, and other causes. Pressure of neoplasms which originate in the brain stem, the cerebellum, or the cerebellopontile angle may prove sufficiently irritating to produce pain which is referred to part or all of the trigeminal distribution.

The trigeminal nerve is apparently particularly subject to so-called *trifacial neuralgia*, which is almost characteristically restricted to the fifth nerve. This disease rests upon no known pathological foundations, for no definite pathological changes have been demonstrated along the course of the nerve, in the ganglion, or in the dorsal root or deep connections of the nerve; it is, however, habitually associated with arteriosclerosis in middle-aged or elderly individuals. The characteristic pain may be referred to any part of the area of distribution of the trigeminal nerve. It usually affects one or more branches of the nerve, but may be limited to one, or affect all three. The pain is usually unilateral. The characteristic feature is the pain which at the beginning is rather dull in character and appears only in paroxysms and for short periods. Between these attacks it is absent. The paroxysms usually become more and more severe, more and more frequent, and longer. The pain becomes sharp and lancinating as if a red-hot needle were driven into the skin or mucous membrane, and may remain localized in one branch or spread to all. It is usually attributed to some abnormality of the teeth, but only rarely can such cause be found.

Usually no objective changes in sensibility can be demonstrated, although rarely hypesthesia or hyperesthesia to touch and pinprick may be observed. The paroxysms of pain may be referred to any or all parts of the trigeminal distribution. They may be brought on by any form of stimulation, brushing the hair or teeth, washing the face, eating, talking, or in some instances merely by a draft of air. The disorder may manifest

itself as confined to the distribution of one division or a part of one division, and later extend to other regions. A similar condition, in which the pain is referred to the fauces and pharynx, seems to depend on some change in the sphenopalatine ganglion, since cocainization of this ganglion may relieve the pain.

Trigeminal neuralgia may also be associated with spasmodic reflex contraction of the muscles of the seventh nerve. It is then called *tic douloureux*. It results from neuritic involvement of the trigeminal nerve, and is associated with a spasmodic, reflex contraction of the facial musculature which gives the condition its name.

Perverted Sensibility (*Paresthesia*).—Irritative lesions of the peripheral branches of the central connections of the trigeminal nerve may sometimes pervert sensation and produce a feeling of tingling, numbness, or formication. These disturbances are often the initial symptom of hypesthesia and anesthesia.

Hysterical Disturbance in Sensibility.—Hysterical disturbances are typically non-anatomical and do not follow any laws in their manifestation. *Hysterical anesthesia*, which is quite common, affects all types of sensibility, is usually absolute, extends with precision to the midline, and may be associated with functional anosmia, ageusia, and amaurosis, with such other hysterical stigmata as loss of corneal and pharyngeal reflexes. The character and distribution of the changed sensation is found to be profoundly affected by suggestion.

Motor disturbances of the trigeminal nerve may be irritative or paralytic.

Irritative.—The irritative type of disturbance is characterized by local or general spasms of the muscles of mastication. It may be associated with irritative lesions in the area of the cortex which controls the masticatory muscles. The symptoms are the local expression of Jacksonian epilepsy. Violent convulsive movements of the jaws are also seen in generalized epileptic seizures, biting of the tongue being one of the most characteristic manifestations. The spasm of the masticatory muscle may be an expression of more wide-spread irritation of the central nervous system. It may be the initial symptom of tetanus or lockjaw. If limited to the jaws it is called "*trismus*." In this the spasms of the muscles occur before other manifestations appear. It is, of course, one of the outstanding features in *hydrophobia*. Hyperirritability of the masticatory apparatus is also a symptom of *tetany*. It also occurs in the chattering associated with chills, or as a result of reflex irritation from the mouth, jaws, or teeth. It is present also in strychnin poisoning.

Other hyperkinetic types of motor trigeminal disturbance appear in paralysis agitans and epidemic encephalitis. In paralysis agitans the typical tremor may be located in the muscles of the jaw and cause a constant or inconstant rhythmical tremor of the jaw. In many of the sequelæ of encephalitis there is involvement of the musculature of the masticatory apparatus. Not only syndromes similar to that of pseudobulbar palsy but also irritative phenomena have been observed, such as grinding, champing, and chattering movements which seem to be due to involvement of the substantia nigra.

Paralytic disturbances may be peripheral or central.

Peripheral.—Paresis or paralysis of the masticatory muscles may result from neuritic conditions which are part of general postdiphtheritic neuritis,

from exposure to cold, or from the reflex irritation of diseases of the teeth and mouth, or caries of the alveolar process. Peripheral disturbances of the motor portion of the trigeminal nerve may also follow inflammation of the portio minor between its origin in the brain stem and its distribution to the muscles of mastication. On account of its close relationship to the mandibular division, lesions often involve both of these divisions. It may also be affected by neoplasms arising from the brain-stem, the neighboring cranial nerves, the meninges, and the skull; and injured by penetrating wounds, fractures of the base of the skull, etc. The existence of unilateral peripheral paralysis may be demonstrated by the voluntary paralysis, the muscles and the floor of the mouth being soft to direct palpation, by the deviation of the jaw toward the paralyzed side, and by inability to move the jaw toward the sound side. The jaw jerk is lost, the muscles atrophy, and the reaction of degeneration appears. Unilateral paralysis disturbs but little the movements of mastication.

Central.—Paralysis of the masticatory apparatus may follow nuclear involvement by the usual types of acute or subacute inflammation, such as encephalitis, either general or epidemic, polio-encephalitis, ascending paralysis, progressive nuclear amyotrophy, or the chronic condition characteristic of tuberculous or syphilitic lesions. Neoplasms of the brain-stem also sometimes involve the masticatory nuclei unilaterally or bilaterally. In bilateral nuclear lesions of the masticatory apparatus the jaw falls and all movements are abolished. The jaw jerk is lost, atrophy takes place in the muscles, and there is a reaction of degeneration.

Involvement of the motor control of the trigeminal nerve is also associated with many types of disease of the cerebral hemispheres. These disturbances often follow definite phases of hyperkinesis. In pseudobulbar palsy there may be bilateral or unilateral involvement of the muscles of mastication. Unilateral interference with these muscles makes difficult the approximation of the jaws on the side of the paralyzed muscles. The lower jaw tends to deviate toward the side of the paralyzed muscles on account of the unopposed action of the unaffected pterygoid muscles. It is therefore difficult to approximate the teeth. The jaw cannot be protruded easily and there is lateral movement only toward the paralyzed side. In bilateral disease the jaws cannot be approximated or protruded, there is no lateral movement, and food falls from the mouth. There is usually no atrophy and no reaction of degeneration if the lesion is supranuclear. The jaw jerk usually remains and is exaggerated.

Paralysis of the mylohyoid and the digastric muscles relaxes the floor of the mouth. This is readily palpable. There may also be asymmetry of the soft palate, the paralyzed side being somewhat lower because of involvement of the levator palati and the azygos uvulæ muscles. This is not constantly present in phonation.

The branches of the trigeminal nerves may be implicated in trauma to the base of the skull with fracture, also by chronic inflammation of the meninges, basilar tumors, aneurysms of the vessels of the base of the skull, thrombosis of the sinuses, and osteomyelitis of the cranial bones.

Progressive facial hemiatrophy has been said to result from peripheral or pontine nuclear disease of certain portions of the fifth nerve. It is characterized by progressive atrophy of the bones, cartilages, and soft tissues of the involved portions of the face, while the muscles show no signs of the

reaction of degeneration. Facial hemiatrophy may follow disease or injury of the fifth nerve. It is usually more intense in the middle and inferior divisions. Conditions which have caused it are injuries to the head and face, infection, exposure to cold, erysipelas, osteitis of the jaw, etc. The nose, chin, and mouth seem to deviate to the affected side. The disease may be progressive for years or may come to a standstill at any time. It does not seem to be definitely modified by any type of treatment.

Henry Alsop Riley.

DISEASES OF THE CEREBRAL NERVES (SEVENTH TO TWELFTH)

The Facial Nerve.—Paralysis.—*Etiology.*—*Facial paralysis* shows no special age or sex relationship, although it but rarely occurs in childhood. In some instances there seems to be a congenital origin. *Facial palsy* may result from lesions situated anywhere from the cortical, facial center in the lower Rolandic region to the division of the nerve trunk in the parotid gland. Lesions of the nerve trunk are the most frequent cause and produce so-called peripheral or Bell's palsy.

Supranuclear and *nuclear facial palsy* may result from tumors, internal capsular hemorrhage, or thrombosis and encephalitic processes. Congenital facial paralysis is usually bilateral and combined with partial or total oculomotor paralysis.

Peripheral facial palsy may accompany gout, diabetes mellitus, tonsillitis, puerperal infections, and diphtheria. It may be affected in multiple neuritis, especially the alcoholic form, and there is a type of syphilitic neuritis of the seventh cranial nerve which occurs in the early stages of this disease. Meningitis, syphilis, tuberculosis, or suppurative processes may involve the nerve at the base of the skull. Tumors of the acoustic nerve, endotheliomata arising from the meninges, and aneurysms and fractures of the base of the skull are other agents which may cause lesions of this part of the nerve. In the Fallopian canal it is involved by diseases of the middle ear and caries of the petrous portion of the temporal bone. Fractures of the base of the skull may produce paralysis immediately, after the interval of a few days, because of inflammatory processes, or later, on account of the pressure of the callus. Operations on the mastoid have at times directly injured the nerve. By far the most frequent cause of facial paralysis is the neuritis accompanying exposure to cold or local chilling. This may be brought about by application of ice to the side of the neck or face, exposure to the draught from an open window or electric fan, or washing the hair. The exact mechanism of this process is unknown, but the long course of the nerve through an unyielding bony canal in which there are a large number of lymphatics is believed to favor pressure neuritis. Herpes zoster involving the geniculate ganglion may be sufficiently intense to involve the motor fibers of the facial nerve. Blows by sharp or dull instru-

ments resulting in direct injury or pressure may cause palsy of the nerve after its exit from the stylomastoid foramen. Stab wounds and injuries from the application of obstetrical forceps also act in this way. Inflammatory processes in the parotid or face or mouth cavity often favor, if they do not directly produce, facial paralysis.

Symptoms.—The *paralysis* comes on rapidly in the course of a few hours without premonitory symptoms. That due to local inflammation, however, may be preceded by the symptoms of the primary disease. At times there is pain in the face or neck, usually behind and below the ear, for a short time before the paralysis appears and for a week or two afterward. This has been attributed to a simultaneous involvement of the local sensory nerves (trigeminal, cervical, and occipital). Well-marked paralysis affects all the muscles supplied by the facial nerve. The disturbance may be first noticed by friends on account of the distortion of the face or because of inability to whistle, puff out the cheeks, or close the eye. The appearance of the face is characteristic. The unaffected muscles draw the *mouth* toward the normal side and elevate its corner. The wrinkles of the forehead and the nasolabial fold on the affected side are flattened out. The eye is more widely open than the other and the lower lid slightly everted so that the mucous membrane is visible. There is a slight deviation of the nose toward the sound side. Voluntary movements—showing the teeth, attempts to whistle, closing the eyes—are possible only on the normal side and greatly increase the asymmetry. As the lips cannot be tightly closed and the corner of the mouth droops on the paralyzed side saliva may escape from the corner of the mouth.

The strength of the muscles may be tested in doubtful cases by attempting to open the tightly closed eyes or to draw back the corners of the pursed mouth by inserting the tips of the fingers into the mouth. If the patient attempts to resist his own inflation of the cheeks, the cheek of the paralyzed side is distended because of failure of the buccinator.

The *eye* on the affected side cannot be closed nor the eyebrow elevated. In attempts to close the eyes the palpebral fissure remains open on account of paralysis of the orbicularis palpebrarum, the upper eyelid is lowered on account of relaxation of the levator palpebræ superioris, and the eyeball turns upward until the cornea is hidden. Since winking and the lid-closure reflex are absent, foreign bodies are apt to lodge on the cornea or conjunctiva and produce inflammation. *Articulation* may be affected in that the labial sounds are defectively formed. Relaxation of the lower lid allows the tears to escape on the cheek rather than through the lacrimal duct. Common sensation is not affected, although taste may be imperfect or absent on the anterior two-thirds of the same side of the tongue. The secretion of saliva on the paralyzed side is usually diminished. The hearing may be modified, so that high notes are not accurately perceived while low notes are more readily heard than on the normal side.

Herpes zoster of the auricle or external auditory canal is occasionally a symptom. The electrical excitability is normal at first, but shortly response to faradic stimulation is lost and, if the process be severe, partial or complete reaction of degeneration develops during the first two weeks.

Diagnosis.—Fully developed facial palsy is recognized at a glance. In order to discover the cause, it is important to determine, if possible, the site of the nervous lesion, whether it is in the tracts leading from the cere-

bral cortex to the facial nucleus, in the facial nucleus itself, or in the pathway from the nucleus to the periphery.

Supranuclear lesions characteristically do not affect the superior facial branches which supply the orbicularis palpebrarum and the muscles of the forehead, or involve them but slightly because they are innervated from both hemispheres; neither do they alter the electrical reactions nor the reflex excitability of the facial muscles; they are frequently associated with hemiplegia of the same side, rarely with that of the opposite side. *Lesions of the nucleous or motor root* within the substance of the pons produce complete paralysis of the same side of the face, but no disturbance of taste; a change in the electrical reactions; loss of reflex excitability in the affected muscles; and frequently, in addition, paralysis of the abducens nerve because of its close anatomical relationship within the pons.

If the nerve is affected between its origin in the pons and the geniculate ganglion the symptoms are similar to those of nuclear origin except that the sixth nerve is not usually affected. The eighth nerve may be involved. Taste in the anterior portion of the tongue is normal. Often the secretion of tears on the affected side is diminished.

If the facial nerve becomes abnormal after leaving the stylomastoid foramen, complete paralysis of the entire side of the face ensues.

The Nervus Intermedius of Wrisberg.—The afferent fibers of the *Nervus intermedius* convey sensations of taste through the glossopharyngeal nucleus to the brain; the efferent fibers join the submaxillary ganglion and transmit secretory impulses to the submaxillary and sublingual glands. R. Hunt has described instances of inflammation of the geniculate ganglion analogous to that of the posterior root ganglia in herpes zoster. The *symptoms* of inflammation of the geniculate ganglion are the eruption of herpetic vesicles in the external auditory canal and pain in the auricle. If the inflammation be so severe as to implicate the motor fibers of the facial nerve, weakness of the facial muscles results and taste is lost over the anterior portion of the tongue. When the auditory nerve is involved, tinnitus, vertigo, diminution of hearing, and possibly nausea and vomiting ensue.

Auditory Nerve.—Paralysis.—*Diseases of the Cochlear Portion of the Nerve.*—Unilateral deafness may be produced by lesions of the temporal lobe. Memory of words heard seems to be located in the first temporal convolution on the left side. Very severe injuries to this area produce *word deafness,* a condition of failure to understand spoken words, although sounds are heard. Injury of the auditory areas of both sides produces complete deafness. Nuclear disease of the auditory nerve is practically unknown. The termination of the nerve is often affected in labyrinthine disease. The nerve trunk is frequently the seat of tumors and may be involved in tumors of the bone or meninges, or by inflammation in the surrounding tissues. Infiltration of the auditory nerve has been frequently observed in leukemia. Toxic neuritis probably develops more frequently in the auditory than in any other cranial nerve. It occurs in meningitis, scarlatina, and typhoid fever. Implication of the auditory nerve is also found in tabes, multiple sclerosis, and other diseases. Hemorrhages and inflammations may affect the labyrinths, either one alone or both simultaneously. This is especially common in syphilis, but may take place in the infectious diseases (typhoid, scarlatina, mumps, influenza, malaria, and meningitis).

Diagnosis.—Loss of function of the cochlear portion of the acoustic nerve impairs hearing. As *disturbances of the middle ear* also produce the same effect, nerve deafness must be distinguished from it by the reduction of hearing through bone conduction and defective perception of the higher notes of the scale. The integrity of bone conduction is determined by Schwabach's, Rinné's, and Weber's tests.

Schwabach's test is carried out by comparing the time during which a vibratory tuning-fork is audible when applied to the mastoid process of the side affected with that on the normal side, or of a normal individual. In the impairment of hearing which accompanies a nerve lesion the period of audible bone conduction is shortened, while in deafness referable to the middle ear this is normal or prolonged. In performing the *Rinné test* a vibrating tuning-fork is placed upon the mastoid process: when the sound is no longer perceptible the fork is held opposite the external auditory meatus. An individual with normal hearing then hears the sound again. This is described as a positive result ("positive Rinné"). In diseases of the middle ear the sound conduction through the air is reduced and consequently the sound is not heard when the fork is opposite the ear ("negative Rinné"). In nerve deafness the test is positive, as a rule, unless there is a marked defect of hearing. The *Weber test* is carried out by placing a vibrating tuning-fork on the vertex of the skull. In the normal individual the sound is heard with equal intensity in both ears. If one ear is artificially occluded the sound is heard loudest in the ear in which the air conduction is thus interrupted. This "lateralization" of sound occurs also on the side of the impaired hearing in individuals with diseases of the middle or external ear (sound-conducting apparatus). This is referred to as a "positive Weber" sign. A person with nerve deafness lateralizes the sound to the normal side ("negative Weber"). The perception of the notes of the scale are tested by Galton's whistle. Deafness for the higher notes of the scale is evidence of nerve deafness rather than of disease of the middle or outer ear.

Tumors of the trunk of this auditory nerve are more common than growths of any of the other cranial nerves. Those occupying the cerebellopontine angle evoke symptoms which render diagnosis easy in many instances. The symptoms are those of internal hydrocephalus (headache, vomiting, and choked disks), and local manifestations such as impaired hearing and loss of function of the auditory nerve, hemiasynergy, cerebellar ataxia, paresis of basilar cranial nerves, especially the seventh, sixth, fifth, and possibly the ninth and tenth, and nystagmus, increased by looking toward the affected side.

Diseases of the Vestibular Portion of the Auditory Nerve.—*Ménière's Disease; Acute Labyrinthitis.*—Ménière's disease is an acute disturbance of the labyrinth, due either to inflammation or to hemorrhage which is caused by various acute infectious diseases, but especially by syphilis or arteriosclerosis. Entire destruction of the labyrinth evokes *characteristic symptoms*—intense dizziness, vomiting, profound disturbance of equilibrium with a sensation of rotation of the body around its long axis, and marked nystagmus. The patient is not able to stand and lies upon the sound side. Turning on the back or other side causes intense vertigo. These symptoms are pronounced for four or five days and then gradually subside, but the nystagmus persists for a longer period, and quick turning of the head may produce vertigo. The disturbance of equilibrium eventually passes away, but tinnitus and impaired hearing or deafness persist.

Chronic Labyrinthitis is usually secondary to disease of the middle ear. Tinnitus and some degree of deafness usually precede the attacks of vertigo, which vary in severity. When severe enough to cause the patient to fall to the ground suddenly with a sensation that external objects are revolving about him, they may be accompanied or followed by vomiting, and nystagmus occurs simultaneously: when less severe the patient reels but can prevent falling by grasping some stationary object. The giddiness may

persist for hours or pass off in a few minutes. The attack is usually followed by nausea and headache, which last for some hours. Between attacks there is some degree of deafness and tinnitus. The symptoms may be unilateral or bilateral. One ear is usually more severely affected than the other.

The disease is not always progressive, although the symptoms may recur from time to time for long periods.

As a rule there is little difficulty in the diagnosis of this malady when the symptoms are severe, but when the aural symptoms are not marked it may be confused with *petit mal*. The absence of complete loss of consciousness and the presence of deafness and tinnitus, however, suggest labyrinthitis rather than epilepsy.

The Glossopharyngeus, Vagus, and Accessory Nerves.—Glossopharyngeal Paralysis.—Isolated paralysis of the ninth nerve has not been observed, for the nerve is so intimately associated with the spinal accessory and vagus that it is not affected alone. Symptoms of glossopharyngeal palsy would include anesthesia of the upper portion of the pharynx, loss of taste over the posterior third of the tongue, difficulty in swallowing, and abolition of the pharyngeal reflex.

Vagus Paralysis.—*Etiology.*—The *medullary nuclei* may be involved in bulbar palsy, medullary tumors, syringomyelia, epidemic encephalitis, lues, and multiple sclerosis. The *intracranial portion* may be affected by growths or inflammatory processes in the meninges, aneurysms, diseases of the bones of the base of the skull, and intracranial hemorrhages. Operations on the neck may injure the vagus, especially ligation of the carotid or the removal of glands or tumors. The vagus is occasionally the seat of neuritis, which has been attributed to the spine in such infectious diseases as typhoid, pneumonia, influenza, and especially diphtheria. Of the chemical poisons, alcohol has the most important action on the vagus, but lead and arsenic may also have some effect. The *recurrent laryngeal branch* is especially prone to injury, and is frequently damaged in removal of the thyroid or in ligation of the inferior thyroid artery. It may be involved in atheroma or aneurysms of the aorta, dilatation of the left auricle in mitral stenosis, tumors or enlarged glands of the mediastinum or neck, and in tuberculosis and other affections of the lungs.

Symptoms.—Total vagus paralysis is seen most frequently in processes which involve the nerve trunk within the skull. If one vagus alone be involved there is unilateral paralysis of the palate, pharynx, and larynx. Frequently also there are evidences of involvement of other cranial nerves, particularly of the glossopharyngeal, the superior root of the spinal accessory, and the hypoglossal nerve. The soft palate does not move on the affected side and is arched lower than on the normal side. The voice assumes a nasal quality and the pharyngeal paralysis may produce a slight difficulty in swallowing. There is absence of the palatal and pharyngeal reflex on the affected side. The corresponding vocal cord is in the cadaveric position and does not move either with phonation or respiration. Disturbances of cardiac rate or rhythm are not constant in unilateral vagus paralysis: there may be slowing of the rate or alteration of the rhythm, but these, as a rule, are not permanent. Symptoms referable to the abdominal branches (vomiting, anorexia, pains, etc.) have been described, but are too inconstant and unreliable to be of value in diagnosis.

The most frequent and important symptom is *laryngeal paralysis*, which

may occur as the only result of lesions of the vagus itself or of the recurrent laryngeal. In unilateral paralysis of the recurrent laryngeal the affected vocal cord is in the cadaveric position, midway between abduction and adduction. It does not move either on phonation or respiration. During phonation, which is carried out fairly well, the healthy cord is moved across the midline and approximated to the paralyzed one. There is some hoarseness, but the quality of the voice is not greatly altered. Respiration is not impeded except on very deep inspiration, when there is some stridor.

The symptoms of the various types of laryngeal palsy are most clearly indicated in Table 1, which is taken from Gowers:

TABLE 1

Symptoms.	*Signs.*	*Lesion.*
No voice; no cough; stridor only on deep inspiration.	Both cords moderately abducted and motionless.	Total bilateral palsy.
Voice low pitched and hoarse; no cough; stridor absent or slight on deep breathing.	One cord moderately abducted and motionless, the other moving freely, and even beyond the middle line in phonation.	Total unilateral palsy.
Voice little changed; cough normal; inspiration difficult and long, with loud stridor.	Both cords near together and during inspiration not separated, but even drawn nearer together.	Total abductor palsy.
Inconclusive; little affection of voice or cough.	One cord near the middle line, not moving during inspiration, the other normal.	Unilateral abductor palsy.
No voice; perfect cough; no stridor or dyspnea.	Cords normal in position and moving normally in respiration, but not brought together on an attempt at phonation.	Adductor palsy.

In *complete bilateral recurrent laryngeal paralysis* the symptoms are complete aphonia, lack of closure of the glottis in coughing, and difficulty in breathing, due not alone to insufficient width of the glottis, but also to the fact that the vocal cords are drawn inward closer together on inspiration, with consequent inspiratory stridor and severe dyspnea. In some instances *central or peripheral injuries* of the vagus affect only the fibers of the recurrent laryngeal which supply only the posterior crico-arytenoid muscles (abductors). This produces narrowing of the glottis to a mere fissure, so that inspiration is stridulous, while the voice is not seriously interfered with. Isolated paralysis of the *superior laryngeal nerves* is very infrequent and is produced mainly by injuries or operations on the neck. The diminished sensation which results in the pharynx and larynx causes a tendency to allow food to enter the larynx, and paralysis of the cricothyroid muscles causes defective approximation of the cricoid and thyroid cartilages in phonation, which results in hoarseness and lowering of the voice and rapid fatigue on intonation.

The Spinal Accessory Nerve.—PARALYSIS.—*Etiology.*—The nuclei or roots of the spinal accessory nerve may be involved in the diseases of the upper cervical region of the cord (poliomyelitis, progressive muscular atrophy, myelitis, gliosis, or tumor). The chief causes of peripheral paralysis are caries of the upper cervical vertebræ, new growths, meningitic exudations, and lesions of the meninges or of the bone in the region of the jugular foramen. In the neck the nerve may be injured by operations

for the removal of cervical glands, in the resection of cervical ribs, by the pressure of tumors, and rarely by primary inflammation of the nerve. Lesions of the base of the skull also frequently affect the vagus and occasionally the hypoglossal.

Symptoms.— The symptoms of paralysis of the accessory portion of the eleventh nerve are entirely motor, producing complete paralysis of the sternomastoid and incomplete paralysis of the trapezius. Inaction of the sternomastoid is shown by inability to turn the head completely toward the opposite side. In bilateral paralysis of the sternomastoid muscles the head tends to fall backward, and in the horizontal position it cannot be raised forward without assistance. Paralysis of the trapezius muscle is made manifest by an alteration of the outline of the neck and drooping of the shoulder. The scapula on the paralyzed side is displaced downward and outward and rotated outward, so that its inner border is inclined from below upward and outward instead of being parallel to the spine. Elevation of the shoulder on the affected side is imperfect and the scapula cannot be actively approximated to the midline.

Hypoglossal Nerve.—Paralysis of the tongue in cerebral disorders is a common result of lesions producing hemiplegia. The nucleus is involved in bulbar palsy and in syringobulbia, and may be affected by tabes and diseases of the medulla oblongata. As the hypoglossal nuclei are placed close together in the medulla, both are involved, as a rule, in medullary lesions, although instances of unilateral nuclear diseases have been recorded. Paralysis of the hypoglossal caused by lesions of the nerve is produced mainly in the posterior cranial fossa (tumors of the brain or meninges, basilar meningitis, hemorrhages, or aneurysms of the vertebral artery). The nerve has also been injured by fracture of the base of the skull, and by carious changes in the bone. It is rarely injured outside of the skull, but may be severed by penetrating wounds or involved in deep abscesses or tumors or in dislocation or caries of the first cervical vertebra. Cortical or supranuclear lesions produce paralysis of the opposite side of the tongue. On protrusion the tongue deviates toward the paralyzed side because of the action of the unaffected genioglossus muscle and the inaction of the paralyzed one. In supranuclear lesions there is no atrophy of the tongue. Nuclear disease usually affects both nuclei, but unequally. The tongue cannot be protruded and atrophies, so that fibrillary tremors develop in the wasting muscles. The roots of the hypoglossal and pyramidal tracts for the opposite side of the body are involved rarely by a single lesion. This produces a crossed paralysis of the tongue and limbs.

Speech is not much affected by unilateral paralysis of the tongue, but is much disturbed in bilateral paralysis, as are swallowing and proper mastication.

HUBERT S. HOWE

DISEASES OF THE SPINAL NERVES

Hiccup.—DEFINITION.—An intermittent clonic contraction of the diaphragm often associated with clonic contractions of the accessory muscles of respiration.

The condition may occur at any age. Sex plays no part. It is due to a great variety of causes which irritate either the afferent pathway to the centers in the upper cervical part of the spinal cord, the centers themselves, or their efferent pathway to the muscles.

The afferent pathway may be irritated by swallowing very hot or irritating substances, and by disorders of the esophagus or of the stomach, such as gastritis and gastric dilatation. Various intestinal disorders may initiate an attack, such as obstruction, ileus, strangulated hernia, acute appendicitis, acute pancreatitis, and typhoid fever. Peritonitis may be the cause. Postoperative hiccup is often very severe, refractory to treatment, and so weakening as to endanger life. The centers may be affected by tumors or meningomyelitis due to such infections as syphilis or epidemic encephalitis. An epidemic variety of hiccup was abundantly reported in Paris in 1920. In some cases no signs of epidemic encephalitis coexisted in these cases; in others, the hiccup was a clonic part of that disease. The attacks did not last over a week. Similar cases have been reported in America.

Tumors and inflammatory disease of the mediastinum, such as caseous glands, enlargement of the heart, and adherent pericardium, are occasional causes.

Uremia and alcoholism—acute or chronic—are toxic causes.

Cancer metastases to the liver may be a cause.

Finally, the condition may be psychogenic in origin. In these cases it often lasts for weeks, but stops while the patient eats.

Treatment.—Pressure upon the phrenic nerve between the heads of the sternocleidomastoids, drinking cold water, holding the breath, or a sudden fright may be tried and will stop a mild attack. Gastric lavage, gr. $\frac{1}{8}$ of apomorphin, or gr. $\frac{1}{100}$ of hyoscin hydrobromate may be tried. Morphin sometimes succeeds. When hiccup is not due to inflammation of the centers (epidemic encephalitis) this is the best remedy. Benzyl benzoate (℥ss of a 20 per cent. solution) sometimes stops an attack. Inhalations of nitroglycerin or chloroform have been used. Application of an ice-bag to the neck, ethyl chlorid sprayed on the epigastrium, repeated traction of the tongue, pressure upon the eyeballs, mechanical dilatation of the esophagus by a small bougie, and pressure upon the ribs near the origin of the diaphragm should all be tried in difficult and refractory cases.

Cervical rib is a development anomaly consisting of a more or less completely developed rib lying above the first thoracic rib and in relation to the seventh cervical vertebra.

The various forms of cervical ribs may exist in two or more members of a family. They usually do not produce symptoms or signs until the third decade. Women are said to be more frequently affected than men.

The anatomical relations explain the disorders which these developmental anomalies cause. The extra rib lies beneath the seventh and eighth cervical roots of the brachial plexus and in close relation to the subclavian artery.

A more or less constant relation exists between the origin of the roots comprising the brachial plexus and the presence or absence of the extra rib. A plexus is said to be prefixed when it receives fibers from the fourth cervical root, a small branch or none from the first thoracic root, and no connecting branch from the second thoracic root. This condition is often

associated with cervical ribs. However, not all cases of cervical rib have a prefixed plexus. A postfixed plexus is one with no fourth cervical root and a very large first thoracic branch and a connecting branch from the second thoracic root. This may be associated with a defective first thoracic rib.

The varieties of abnormal ribs are five (Sargent):

"(1) An exaggerated costal process of the seventh cervical vertebra not jointed to but fused with the transverse process, and continued forward and downward as a fibrous band to be attached to the first thoracic rib behind the scalene tubercle.

"(2) A short rib articulated to the seventh cervical vertebra by costocentral and costotransverse joints, and continued onward as a fibrous band to be attached to the first rib as in Type 1.

"(3) A jointed rib of sufficient length to carry the eighth root upon its bony portion and attached by a fibrous band to the first rib.

"(4) A jointed rib of which the anterior extremity makes contact with the first thoracic rib, the two either being fused or united by an irregular articulation.

"(5) A rudimentary first thoracic rib, the anterior fibrous portion of which is attached to the sternum, usually by a rudimentary costal cartilage."

The ribs may be bilaterally symmetrical or asymmetrical; but one side may produce a visible prominence. They may very often be felt. *x*-Ray examination establishes their presence. Though ribs may be found on both sides, but one side may produce symptoms.

The relation of these various anomalies to the subclavian artery and its branches is of importance. The extra rib either lies upon the first thoracic rib or upon the fibrous band of the cervical rib. The transversalis colli or suprascapular artery may lie upon the cervical rib.

The sympathetic system sends fibers from the first thoracic and inferior cervical ganglia to the plexus. As the signs and symptoms indicate, these may also be affected by pressure of the extra rib or its fibrous continuation.

The cause of the appearance of signs and symptoms is sudden and severe or long-lasting and oft-repeated compression of the nerve roots, as in carrying very heavy weights upon the shoulders, continual irritation of the root by respiration, the effort of childbirth, and the drooping of the shoulder after adolescence. Other causes, such as periostitis, have been described.

Signs and Symptoms.—These are motor, sensory, and vasomotor. The decision as to what roots are affected when these various manifestations are found is not merely a question of knowing the classical segmental or radicular innervations of muscles and skin. The contribution to these muscle and skin areas by roots varies according to the form of plexus, prefixed, normal, or postfixed. Thus, for example, in a prefixed plexus (often associated with cervical rib) the eighth cervical root supplies all of the intrinsic hand muscles and the ulnar side of the skin of the hand and forearm.

The motor manifestations are weakness, atrophy, and various degrees of reaction of degeneration. These are usually found in the muscles supplied by C 8 and D 1, but muscles supplied by the entire plexus may be affected. Occasionally, after carrying heavy weights, an isolated paralysis of the serratus magnus muscle may occur.

The objective sensory changes may correspond to the radicular limitations of the motor changes, but more often they are more limited in extent or quite absent. Subjectively the patient has pain (neuralgia) or paresthesia or both in the forearm and hand. These may be due in some cases to sympathetic nerve involvement.

The vasomotor signs are cyanosis, coldness, or edema, due to pressure upon the sympathetic fibers in the plexus. These changes may become very severe and present the picture of early Raynaud's disease. Paralysis of the cervical sympathetic (Déjerine-Horner syndrome) is very rarely seen.

There may be visible arterial pulsation due to pressure upward of the subclavian or one of its branches. Thrombosis may occur in the artery distal to the rib. The pulses may be unequal.

Congenital syringomyelia is not infrequently associated with cervical ribs. A developmental defect has occurred in both the bony and nervous structures.

The DIAGNOSIS is best made by *x*-ray examination, though occasionally a fibrous band alone may be present, may not show in the *x*-ray film, and may cause as serious disorders as the bony ribs themselves.

The differential diagnosis from the various diseases causing pain, paresthesia, weakness, muscle atrophy, and vasomotor disorders is usually not difficult even without *x*-ray examination. Brachial neuralgia is not complicated by motor signs and symptoms. The pain radiates from and through the shoulder as well as down the arm. Brachial neuritis has a more wide-spread and uniform distribution of signs and symptoms. Progressive muscular atrophy is not complicated by pain or other sensory disorders. Syringomyelia presents a more difficult problem, particularly when the vasomotor trophic disorders of this disease are mildly present. The systematic examination of the reflexes throughout, and of sensation, for the syringomyelic dissociation, should make the differentiation simple. Of course when both cervical ribs and syringomyelia are present the need for differentiation is superfluous.

Spinal cord tumors sufficiently large to cause the signs and symptoms of cervical rib produce other signs and symptoms. Pain in cardiac disease such as that radiating down the left arm is unassociated with vasomotor and motor disorders.

TREATMENT.—Elevation of the shoulder and rest constitute the best initial treatment. Removal of the extra rib, though a serious undertaking, has resulted in cure or marked improvement in many cases. The sensory disorders are often relieved at once. The atrophy disappears much more slowly. Massage and electrical stimulation are indicated after operation. The absence of evidence of a cervical rib on *x*-ray examination is not to be regarded as a final indication against operation if the clinical picture certainly indicates pressure upon nerve-roots.

Radiculitis.—DEFINITION.—An inflammation of a spinal root.

The spinal root on emerging from the spinal cord is not fused into one structure, but is divided into rootlets. Each of these is covered by a layer of the arachnoid continuous with the pia. These cuffs of endothelial cells extend outward to the point of fusion of the anterior and posterior roots. They thus form little troughs in which infection can most easily find a

resting place. Outside of the arachnoid lies the dura, which extends outward and is continuous with the perineural sheaths of the nerves. The root may be defined as the emerging fibers from the point of their emergence from the spinal cord to the point of their fusion into the anterior and posterior roots.

Etiology.—Radiculitis is almost always dependent upon the occurrence of a meningitis, and may therefore result from any of its forms. Among these are syphilis, tuberculosis, acute coccal varieties, and more rarely the exanthemata. The symptomatology of *meningitis* is essentially that of *radiculitis plus signs and symptoms due to increased amount and pressure of spinal fluid.* The symptomatology of meningitis usually given is in reality that of encephalomyelomeningitis, a combination of the symptoms of infection of the brain and spinal cord and those of infection of the meninges. Included in the latter are those of radiculitis. A rare cause of radiculitis is hemorrhage of a root blood-vessel due to arteriosclerosis. A more frequent cause is trauma to the spine. Not infrequently only radicular signs and symptoms are found. Radicular syndromes dependant upon epidemic encephalitis, extramedullary tumors, cancer metastases, Pott's disease, or other forms of spondylitis are not infrequent. They are rarely simple, but complicated by other signs and symptoms elsewhere in the body. Tabes dorsalis at its onset is but a polyradiculitis. The radicular signs and symptoms due to increased spinal fluid pressure in tumors of the brain is considered under that subject.

The disease may be acute, subacute, or chronic.

Symptoms.—The signs and symptoms of radiculitis are sensory, reflex motor, vasomotor, trophic, and glandular.

(1) *Sensory:* The most striking and frequent sensory symptom is pain (neuralgia). It may be extremely severe and lancinating, or dull and aching. It occurs in the area of distribution of the roots involved. It is often referred to as "inside." The points of emergence of the nerve trunks are not tender. Pressure upon muscles does not increase the pain. Coughing, sneezing, or yawning increases the pain by the increase in spinal fluid pressure. Movements which stretch the roots also increase the pain.

Sensations of pins and needles, formication, heat, and cold also occur in areas of root distribution.

Objectively there are sensory losses of various kinds; touch, pain, heat, and cold, always in a radicular distribution. Proprioceptive sensation is uncommonly affected. The entire root distribution may not be completely affected, nor are the areas of several roots always completely affected as may be realized from the description of rootlets given above. Patchy involvement therefore results. In oculomotor paralysis from syphilitic basal meningitis, partial lesions due to involvement of some rootlets only are almost the rule.

(2) The reflexes both deep and superficial are occasionally exaggerated at the onset. Later they are diminished or absent. Babinski's sign and other similar signs, as well as clonus, are absent. The spinal cord is not affected.

(3) Motor disorders are not as common as sensory disorders. They consist of paresis or paralysis and atrophy of the muscles supplied by a root. The electric reactions may show various degrees of reaction of degeneration—rarely complete. Simple diminution of reaction to faradic

and galvanic current is frequent. In lesions of the eighth cervical and first thoracic roots there may appear the syndrome of cervical sympathetic paralysis.

(4) Trophic disorders occur in the chronic varieties. The skin may become more hairy or smoother. Glossy skin may result. The nails become rigid and curved. There may be hyperostosis on the bones supplied by the affected roots. Perforating ulcers may occur. Cyanosis, coldness, paleness, and various disorders of sweating may occur. The spinal fluid changes are those of the cause. There is no special syndrome of radiculitis.

Diagnosis.—The diagnosis is simple by elimination of evidence of *encephalomyelitis* on one hand, *neuritis* on the other. The latter shows tender points at the emergence of the nerves beneath the skin (Valleix's points), a neural distribution of motor and sensory changes, and no evidence of increase of pain by root stretching or by increased spinal fluid pressure brought about by coughing, yawning, and sneezing.

Prognosis and Treatment.—The prognosis depends entirely on the effectiveness of the treatment of the primary cause. Symptomatic treatment for pain demands counterirritation, morphin, codein, pyramidon, or phenacetin. Epidural injections of saline aid temporarily in lumbosacral radiculitis. High-frequency currents may give some relief.

W. M. Kraus.

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HERPES ZOSTER

Definition.—Herpes zoster is a disease due to inflammation or irritation of the posterior root ganglia or the sensory extramedullary ganglia of the cranial nerves. It is popularly known as "shingles."

History.—It was first described as an infectious disease by Von Barensprung in 1863. It has been recognized as a disease since the days of the Greeks, who called it "zona."

Etiology.—The cases may be divided into two groups—essential and symptomatic. Essential herpes zoster is an infection often occurring in epidemics. Evidence, both clinical and bacteriological, has accumulated to show that its cause is identical or very closely allied with that of chickenpox. The symptomatic group may be divided into two subgroups: one comprising about two-thirds of this group, due to cerebrospinal syphilis; the other due to a variety of causes, such as the common infectious diseases of the nervous system, such as myelitis and syringomyelia, spinal extramedullary tumors, diseases of the vertebra (Pott's disease), metastasis to the vertebræ of sarcoma of the prevertebral glands, and, finally, arsenic poisoning. The

average amount of arsenic which will produce herpes is 2 grains, taken in the usual dosage during a period of weeks.

The organism causing the essential group has not been isolated. Its relation to the organism causing chickenpox has been pointed out.

Morbid Anatomy.—The pathological picture in the nervous system is that of inflammation of the posterior root ganglia. Usually several are affected. The first stage is leukocytic invasion; the second, degeneration of the ganglion cells; the third, a fibrous replacement. The dorsal part of the ganglion is affected. The lesion causes a degeneration of some of the posterior root and the peripheral nerve-fibers. The anterior horns are sometimes affected by the inflammation.

The skin lesions begin as erythematous patches occurring in the distribution of the cutaneous nerves. These soon change to vesicles. The contents of the vesicles, first clear, soon become cloudy. If infected, gangrenous areas result. After healing, a scar or pigmented spot often remains. In the young these disappear. They may remain in older individuals.

Signs and Symptoms.—The initial symptom is pain, diagnosed as neuralgia. It is severe. Its distribution is limited to that of one to four or five nerves. If the case is of the essential variety, symptoms of an acute infection occur—malaise, fever, tachycardia, chills. In the symptomatic variety these symptoms are absent and pain alone is present. Within a few days the skin lesion appears. The febrile symptoms disappear. The pain remains in cases of both groups. The lesions first appear near the point of emergence of a nerve. They spread and may overlap each other, causing large lesions. In from two to seven days the rash is out completely. The spinal fluid may show increase of cells and globulin; the blood, a leukocytosis up to 14,000. After about two weeks the lesions begin to heal, scabs form, and then fall off. Scarring or pigmentation may result. The postherpetic stage is characterized by neuralgia. As a general rule the older the patient, the more persistent the pain. It may last for months or years. In children the pain may be absent throughout.

The majority of cases affecting the nerves of the trunk and extremities occur in the thoracic region. The cranial nerves may also be affected. Herpes ophthalmicus is not uncommon. It involves the first branch of the trigeminal and is usually a serious condition causing severe pain, lacrimation, and photophobia. The eruption follows the same course as elsewhere except that it may cause severe corneal ulcers. Such cases should be under the care of an ophthalmologist. The possible residua are pain, which follows the same rule as in herpes in other locations, and ptosis. Herpes of the other cranial nerves—seventh, eighth, ninth, and tenth—is rare.

Diagnosis is not difficult except in the stage before the rash appears. The eruption is quite characteristic. In young people in whom the rash involves more than two or three segments, chickenpox may be thought of. Cases diagnosed as extensive herpes or chickenpox of unusually limited extent have been recorded fairly often. Neither disease often affects the soles or palms, so that the distribution is not of great value. The determination of essential herpes is usually not difficult. The onset with febrile symptoms, and the history of exposure to another case, or a case of chickenpox, establish the essential type. A Wassermann test should be carried out in all cases. It is noteworthy that herpes may be the only neurological sign of a cerebrospinal syphilis, and herpes from this cause is relatively frequent.

The symptomatic variety often recurs, and its course is longer than that of the essential type. The patient should be questioned as to drugs—arsenic.

Treatment.—The pain in the acute stages should be relieved by codein in $\frac{1}{2}$-grain doses given every four hours. The skin lesions should be covered with collodion. If ruptured, an ointment of 1 per cent. cocain in lanolin is advisable. The postherpetic neuralgia may be very refractory to treatment. Aspirin, pyramidon, and codein may be tried. The syphilitic variety is treated by arsenicals or by mercury, given by mouth while the rash is severe, by ointment later.

Severe intractable root pain occasionally has to be treated by posterior root section.

W. M. Kraus.

General and Functional Diseases

PARALYSIS AGITANS

(Shaking Palsy, Parkinson's Disease)

Definition.—Paralysis agitans is a chronic organic affection of the central nervous system characterized by progressive weakness and rigidity of muscles and spontaneous tremor. It represents a fundamental type of motor paralysis, referable to the corpus striatum and extrapyramidal motor system, and bears the same relation to the striospinal system that spastic paralysis does to the corticospinal system. There is a *primary essential form* due to atrophy of cells, and a *secondary* or *symptomatic form*, produced by inflammatory and neoplastic lesions.

Etiology.—There is no recognized specific cause. The essential factors are degenerative changes in the ganglion cells and blood-vessels of the corpus striatum. The disease occurs most frequently in the fifth decennium, but is encountered at all ages. *Juvenile*, *presenile*, and *senile* types are recognized. It is sometimes hereditary and rarely familial. The incidence is about twice as high in men as in women.

Occasional exciting causes are *depressing emotions*, *physical exhaustion*, and *injuries*. Although slight injury is known sometimes to precede the development of tremor, the relation of cause and effect is very doubtful. *Acute infections* may also precede the onset of the disease, and also syphilis.

Morbid Anatomy.—Paralysis agitans is an organic disease of the corpus striatum which produces functional disturbance in the extrapyramidal motor system. In the primary essential form the large motor cells of the corpus striatum become atrophied (atrophy of the pallidal system); in the symptomatic forms the motor neurons are destroyed by vascular, inflammatory, and neoplastic lesions.

The syndrome is a frequent sequel of encephalitis lethargica, referable to localization of the inflammatory process in the corpus striatum and subjacent structures.

Symptoms.—The cardinal symptoms of paralysis agitans are paralysis,

rigidity, and tremor. Variations in the clinical picture depend on the distribution, extent of involvement, and the severity of these fundamental manifestations. In the common form of the disease all three symptoms are simultaneously present; in other cases, however, one may dominate the clinical picture or even exist alone. There is a rigid type, the paralysis agitans *sine tremore*, and a rare tremor form, the paralysis agitans *sine rigiditate*.

The onset of the disease is insidious and, as a rule, progress is slow and gradual. The first symptom may be a *fine rhythmical tremor* of the hand or fingers, which is at first slight and inconstant, but soon becomes permanent and continues during rest. Associated with the spontaneous tremor is a peculiar *weakness and stiffness of the movements of the fingers*, associated with reduction of the gross motor power. The stiffness is wax-like in quality and interferes with the finer movements of the parts. The tremor, weakness, and rigidity very gradually increase in severity and eventually appear in other members. Usually the leg is involved after the hand on the same side, so that the condition assumes a hemiplegic aspect. All variations in distribution occur, and symptoms may appear first in one of the legs, or may pass from one arm to the opposite leg.

Quite commonly, weakness and rigidity are the only evidences of the disease. This rigid type is encountered, according to some statistics, in about 20 per cent. of the cases. Rarely the tremor is present alone, usually only at an early stage. Sooner or later evidences of weakness and rigidity become manifest.

Tremor.—The tremor is rhythmical and ranges from four to seven vibrations a second. The characteristic persistence during rest and the peculiar interosseal posture of the hand and fingers together produce the characteristic pill-rolling movement. Tremor most frequently appears in the upper extremities—especially the hands and fingers—but is also seen in the legs, the head, the jaw, and rarely in the tongue and eyelids. Tremor of the vocal cords has also been described. The tempo is the same in all parts affected, although it varies from time to time under psychic stress or excitement. Tremor diminishes or ceases, as a rule, during voluntary movement; and may be inhibited by a strong effort of the will, although it tends to overflow and appear with greater intensity in one of the other members. It practically ceases during sleep. In the late stages of the disease the tremor lessens, but usually remains manifest in some portion of the musculature. Development of hemiplegia usually causes cessation of the tremor. The tremulousness and wax-like rigidity of the hand are revealed in the hand writing, which is small and wavy (micrographia).

Rigidity, like tremor, begins locally, and gradually becomes generalized. The hypertonicity of the musculature has a plastic quality. In advanced conditions the muscles have a firm, wax-like consistency, and their contour is sharply outlined beneath the skin. To passive movement there is a smooth, waxy resistance, which is interrupted by a rhythmical tremor-like oscillation. This is the *cog-wheel symptom*, and is a latent expression of the inherent tremor tendency.

The general rigidity causes mask-like facies (Parkinsonian mask) and an attitude typical of the disease, which is characterized by slight, generalized flexion of the head, trunk, and extremities. The fingers are held in the interosseal position, with flexion of the basal and extension of the distal

phalanges. In advanced stages the thumb is turned into the palm, and the fingers are flexed into a fist. One curious feature of the disease is the infrequency of movement. Patients sit motionless by the hour, and even the winking reflex is lessened.

Paralytic Disturbances.—The paralysis affects chiefly the automatic and associated movements of the body. The *motor activities* concerned with walking, running, sitting, rising from a sitting posture, and turning in the recumbent posture suffer early involvement. The *facial expression* is stolid and does not change with the emotions of sorrow, joy, and anger. Gestures and similar types of movement, which automatically accompany any social intercourse, are also absent. One of the most characteristic features is that the arms are held stiffly and do not swing alternately in walking. On making a fist the fingers are flexed, but without the sharp associated extension of the wrist which is normal. In walking there is also no associated flexion of the thigh, knee, and foot which accompanies the normal act of stepping. Instead, the foot hangs as the knee is lifted, and emphasizes the slow dragging movement and shuffling gait so characteristic of the disease. There is also a peculiar tendency to *festination*, which is characterized by progressive acceleration of the step and pitching forward of the body, so that the patient breaks into a shuffling run and is only able to stop his precipitate progress by throwing himself against some object in his path. Propulsion, as this is sometimes called, may also take place backward and to either side (retropulsion and lateropulsion). In advanced cases, if the patient is suddenly pushed over while standing on a large mattress, the fall is passive and unaccompanied by those involuntary muscular attempts to break the fall which are present in all other forms of palsy, even in profoundly spastic states.

The preservation of *specially acquired movements* of cortical origin is in striking contrast to the loss of those of the automatic and associated type. Acquired movements are carried out quite correctly in every detail except for the abnormalities imposed by the tremor, rigidity, and paralysis of associated movements.

Purely reflex acts like swallowing are not affected, and in advanced cases, with complete anarthria and general rigidity, solid and liquid nourishment may be ingested by pure reflex deglutition. The *tendon reflexes* in the early stages of the disease are normal or exaggerated. As the rigidity develops they usually diminish, but are never abolished. The *skin reflexes* are preserved and normal. It may be difficult to elicit *abdominal reflexes* because of the marked rigidity of the musculature. The Babinski reflex is not present in uncomplicated cases.

Sensation is not affected, although subjective disturbances are not infrequent (rheumatoid pains, sensation of heat, and burning). There is often flushing and a tendency to *hyperidrosis*.

In many patients a slight elevation of *temperature* is noted, which may depend on the constant, rhythmical tremor and the close relationship between muscle contraction and heat production.

Sialorrhea may be a comparatively early symptom, and is quite frequent in the late stages. Some observers have noted occasional trophic disturbances of the skin and its appendages. The various secretory, vasomotor, and trophic symptoms are neither constant nor characteristic, and are to be regarded as secondary and not primary manifestations of the disease.

The *intelligence*, as a rule, is not affected. Any impairment is due to senility or arteriosclerosis. When a psychosis occurs, it is probably a complication and not an essential symptom. Disturbances of emotional tone are not uncommon, and insomnia, depression, and irritability are frequent symptoms.

Diagnosis.—Recognition of the disease is usually easy. The rhythmical tremor of the hands persisting during rest, the general muscular rigidity, the mask-like expression of the face, and the peculiar posture, together with the absence of all signs of involvement of the pyramidal tract, constitute a syndrome which is unmistakable. It must not be forgotten, however, that the disease appears in both rigid and tremor form. *Multiple sclerosis* is characterized by an intention tremor, and muscular rigidity, if present at all, is of the spastic type and associated with exaggeration of the tendon jerks, clonus, and the Babinski reflex. *Progressive lenticular degeneration* may resemble the presenile form of paralysis agitans, but runs a more rapid course, is attended by fever and emaciation, and often associated with choreiform and athetoid movements which are foreign to the syndrome of paralysis agitans. *Senile tremor* may also cause uncertainty, especially because paralysis agitans is very apt to develop upon this soil. Senile tremor, however, affects chiefly the upper extremities, quite frequently the head, and is increased during movement. The speech may also be tremulous. There is no muscular rigidity, and the peculiar postural changes of paralysis agitans are absent. *Cerebrospinal arteriosclerosis* may produce a syndrome simulating paralysis agitans, especially when the vascular lesions are in the corpus striatum. It is usually possible, however, to demonstrate other symptoms which are foreign to paralysis agitans (acute apoplectiform seizures with hemiplegia, disturbance of sphincters, evidence of involvement of the pyramidal tract, cerebellar symptoms, etc.). The syndrome of paralysis agitans is a common sequel of *epidemic encephalitis*. It may appear months or even years after the initial attack, which may have been mild. The history of a previous attack of encephalitis lethargica and other symptoms referable to the central nervous system (*e. g.*, chorea, athetosis, psychotic manifestations) usually makes the diagnosis clear.

Prognosis.—The course of the disease is slowly progressive, but the patient may live for many years. When the affection appears in young adults, it may persist for two or even three decades. The condition is incurable. At best only the progress can be arrested and some of the distressing symptoms ameliorated. Death results not from the disease itself, but from general reduction of the physical strength and vitality, with consequent predisposition to intercurrent complications and disease.

The course and termination of the secondary or symptomatic forms depend on the nature and extent of the underlying lesion. If due to encephalitis or hemorrhagic and thrombotic lesions of the corpus striatum there is improvement after the acute stage has passed. The rare syphilitic lesion responds to specific therapy.

Treatment.—The treatment is essentially symptomatic. There is no known specific or curative agent. Although the disease is incurable, much can be done to ameliorate the condition and relieve distress. All possible measures should be taken to improve the *general health* and *strength*. The *environment* should be as quiet as possible, because these patients are very susceptible to the least excitement or stress. *Massage, passive movements,*

and *mild exercises* are helpful when given by a skilled attendant. Care should be exercised to avoid fatigue or exhaustion. *Electric baths* are helpful and temporarily diminish the rigidity; general vibratory massage with the electric vibrator also tends to reduce stiffness and prevent the development of deforming postures. In some cases, static electricity has proved of temporary benefit, probably as much for psychical as physical reasons.

For the tremor, *hyoscin* and *hyoscyamin* are recommended. For sleeplessness and the distressing heat and burning, mild hypnotics should be given. Codein and morphin may be employed only in exceptional cases, as a habit is readily formed, which in the end only adds to the distress and suffering.

J. Ramsay Hunt.

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ACUTE CHOREA

(St. Vitus' Dance, Sydenham's Chorea)

Definition.—Acute chorea is an acute, infectious disease characterized by involuntary, coarse, muscular twitching, psychical changes, and a propensity to endocarditis and polyarthritis. It is usually seen in children, but in rare instances occurs in adults. It is more common in cities than in the country, and chiefly affects the poorer classes.

Etiology.—The recent suggestion that acute chorea is a clinical manifestation of epidemic encephalitis seems less correct than the older conception of the condition as a disease entity. Although this type of chorea seems to be frequently associated with certain physical or psychic states, the exciting agent is thought by many observers to be a non-hemolytic *streptococcus*. This organism probably produces toxins, which, by acting on the brain and basal ganglia, produce the symptoms characteristic of the disease. The facility with which these are produced varies under different conditions. *Fright* or *trauma* may precipitate or exaggerate an attack; and *emotional shock* seems to play a noteworthy rôle in the production of relapses when a *locus minoris resistentiæ* has been established. In children *mimicking* may produce a habit spasm, but not true chorea.

Age.—In the decade between five and fifteen years of age the susceptibility to acute chorea is greatest. Rarely the disease is seen in infants or even at birth, but 80 per cent. of all cases occur during childhood. Adults

are rarely affected except during pregnancy. The senile type of chorea is usually a symptom of some other organic disease of the brain.

Sex.—Girls are more susceptible than boys. Statistics show that the relative incidence is 2.5 : 1.

Season.—The seasonal occurrence is a matter of disagreement between different investigators. Gowers' figures show that the incidence is highest during January, February, and March, lowest during July, August, and September; while Lewis has found it highest in March and lowest in November.

Heredity is an etiological factor probably merely because it is responsible for peculiar vulnerability of the nervous system or for susceptibility to rheumatic infection, and not because it permits direct transference of the disease itself. Race is probably more important than individual inheritance, however, for certain peoples appear to be relatively immune—full-blooded American Indians, for example, and negroes.

Pregnancy predisposes to acute chorea, and favors a relapse in previously choreic individuals. Attacks are most common during the third month of the first pregnancy in women less than twenty-five years of age. Much so-called chorea of pregnancy is hysterical mimicry.

Acute Infections.—Various acute infectious diseases (particularly measles and scarlet fever) may modify and coincide with acute chorea, although they play no directly causative rôle.

Rheumatism *per se* is not really a cause of chorea; it is rather part of a multiple symptom-complex (rheumatism, endocarditis, chorea) caused by a specific virus. It is reported by Strong to have definitely developed before the onset of chorea in 20 per cent. of his cases and to have been at least suspected in 34 per cent. The actual causative agent is possibly a streptococcus or streptodiplococcus which is responsible for the rheumatism, endocarditis, or chorea, alone or together. Rosenow concludes that chorea is due to a streptococcus with peculiar neurotrophic, immunologic, and other properties, and Floyd suggests "that the teeth and tonsils in all probability offer two portals of entry to the body for streptococci in producing any one of these clinically grouped diseases" (endocarditis, acute articular rheumatism, and chorea).

The reflex irritation from *intestinal worms* has been mentioned as a possible but rare contributing cause.

Morbid Anatomy.—The lesion is a low-grade *meningo-encephalitis* which is thought to be so localized that it evokes specific movements. Certain authors believe and others do not believe that there is a difference between the lesions of Sydenham's chorea and choreiform epidemic encephalitis. Marie and Trétiakoff in 1920 reported finding lesions in a case of supposed chorea identical with those associated with epidemic encephalitis. No endocarditis was present, and it is quite possible that this was not Sydenham's chorea, but atypical epidemic encephalitis with choreiform symptoms.

In cases of acute chorea studied by Wilson and Winkelman, the only lesions in the brain were such *congestive changes* as are attributable to any acute infectious disease; this is in marked contrast to Huntington's chronic chorea, which produces marked atrophy of the caudate and lenticular nuclei. In fatal cases of acute chorea, diplococci have been recovered from both the pia and the perivascular canals of the brain. *Hyperemia*

and *thrombosis* may be apparent in the central nervous system and meninges, without uniform localization in the basal ganglia or elsewhere. *Cerebral emboli* have been found, but are not responsible for the characteristic symptoms. Dana states that the meninges and cortex are more involved when the condition is maniacal. Examination of the cerebrospinal fluid is usually negative; a mild pleocytosis may be found, and increased tension. In the blood the average eosinophil count has been reported by Berger to be 7.6 per cent.

Symptoms.—The *onset* of the disease may be gradual or comparatively rapid. It is frequently accompanied by headache, anorexia, and constipation, and occasionally by vomiting. Fever, which is usually of low grade, develops in practically all cases. The severity of the disease varies greatly.

There are three *cardinal symptoms:* spontaneous movements, ataxias, and weakness, to which may well be added a fourth, psychic changes. The patient typically makes involuntary but conscious muscular jerks and twitches. He cannot co-ordinate movements normally, and is unable to hold a muscle or muscle group in steady contraction; he tends to overreach the mark (dysmetria) in pointing tests, and suffers some loss of muscular power. Generally these signs vary in degree on the two sides of the body. There is also a noticeable psychic alteration, frequently dulled perception, diminished attention, or a tendency to hypomania.

The typical *twitching movements* are rather quick and of moderately wide excursion. Each begins suddenly and passes rapidly, and often resembles a gesticulation or grimace. They are not rhythmical: one or several movements in one direction are followed by movement in the opposite direction, but no two are of the same extent. The rapidity of choreic movement is greater than that of athetosis and less than that of a tic. The movements generally cease during sleep, but not in severe cases. In the most severe conditions they entirely prevent sleep. Sensory stimuli may increase them. It is common, during the examination, when the disturbance is mild, for choreic movements to be absent at first; later, when the novelty of the procedure wears off and the patient's attention lessens, the involuntary activities gradually appear, as though they broke through conscious restraint.

Ataxia of the extremities produces stumbling gait, mumbling speech, dysmetria, and asynergia in attempting to perform such complicated acts as piano-playing. Hypotonia is generally well marked. The inability to maintain a tonic muscular contraction is quite typical of the disease, and is readily demonstrated by the patient's handgrip, which tends to relax suddenly and involuntarily. Electromyograms graphically record this peculiarity.

Weakness may be evidence of disturbance in the pyramidal tract. The other motor signs can be referred to lesions in the extrapyramidal, basal ganglial, and cerebellar systems. Very marked weakness produces the paralytic type of chorea and not the common spasmodic type. Varying degrees of involvement of different systems explain the dissimilar symptom-complexes. In each individual the symptoms remain fairly constant in type throughout the course of the disease. Extrapyramidal signs are characteristic of chorea, but pyramidal signs apparently do occur. Extension of the great toe (Babinski sign) is far less common than flexion; the deep reflexes are characteristically diminished, but occasionally increased.

Dana describes a *tonic reflex* evoked by tapping the patellar tendon: the foot flies up and remains up unusually long, or a second reinforcing jerk occurs. In most cases the tendon reflexes and muscle tone differ appreciably on opposite sides of the body.

Acute chorea may involve a single muscle or the entire musculature of the body. Symptoms generally begin in the hands and arms, then involve the face, and later the legs. Often certain facial muscles alone are involved. The tongue is said frequently to continue choreic jerking after the other muscles function normally. As with the deep reflexes, there is a strong tendency for the choreic movements and other motor disturbances to be unilateral. Pure hemichoreas have been reported. In practically all patients the intensity of the twitching varies on the two sides of the body.

Speech is involved in about 25 per cent. of patients. The abnormality is not a paralysis, but a disorder of articulation. It may amount to hesitancy, incoherence, or even transitory mutism.

The *pupils* are often dilated, although they react normally as a rule. Oppenheim mentions hippus as a symptom. There are no trophic changes nor endocrine sequelæ. The electric excitability of nerves and muscles is normal or slightly increased. The sensory findings are negative, except that occasionally there are pains and tenderness in the limbs.

Most choreic patients suffer *psychic alterations* of some degree. Before the typical motor signs appear the disposition frequently becomes irritable; later the dulness, inattention, carelessness, and loss of memory may be so pronounced as to suggest mental deficiency. Mild emotional disturbances are usual, and violent hysterical outbursts occasional. In the more severe conditions, exhaustive psychoses (*chorea insaniens*) may develop, with wild movements, great mental excitement, delirium, visual hallucinations, and delusions. A diagnosis of chorea cannot be made, however, from the psychosis alone. Severe insanity is uncommon, and the 20 per cent. of psychotic patients reported by Hammes from a series of 88 evidently had many mild mental conditions. Pregnant women are especially prone to the more serious mental complications.

In addition to the nervous symptoms, special attention should be directed toward the throat, joints, and heart. *Pharyngitis* or *tonsillitis* frequently complicates some stage of the choreic attack. *Carious teeth* are often found. *Articular inflammation* usually precedes the chorea. *Cardiac complications*, on the other hand, are more likely to appear after it is established or during its involution; tachycardia, whether functional or organic, commonly occurs simultaneously.

Duration and Termination.—Although the duration of acute chorea varies greatly, it is roughly from one to six months. The average in America is from ten to twelve weeks. Poynton, in England, estimated it at six weeks, but admitted that three months is common. Between 15 and 50 per cent. of all initial attacks are followed by one or several recurrences. The disappearance of symptoms is very gradual. Speech defects disappear completely. Very exceptionally acute chorea becomes chronic, or is succeeded by a tic. The prognosis during pregnancy is most unfavorable; the disease tends to persist until the uterus is evacuated, and may continue into lactation. The death rate is about 20 per cent. In non-pregnant patients fatalities are rare (1 to 2 per cent.), and are due more often to the

cardiac than to the neurological condition. In a maniacal state (*chorea gravis*) death may nevertheless ensue without cardiac complication. Paralytic acute chorea runs the same course as the spasmodic type.

Diagnosis.—Sydenham's acute chorea is a disease entity, which must be clearly differentiated from the chorea dependent on diseases unrelated to rheumatism. The following diseases may present some diagnostic difficulty:

Hysteria, protean as its manifestations are, may readily simulate chorea. The history of the disease, the general appearance of the patient, and the lack of physical abnormality should suggest hysteria. This condition is more common at puberty, begins more suddenly, evokes more purposeful and rhythmic movements which are closely localized, and is usually associated with anesthesia and analgesia.

Tic, or *habit spasm*, is still more localized; abrupt, momentary contractions affect single muscles or groups of physiologically related muscles. Such movements are co-ordinated and purposeful, and remain the same in repetition. Choreic movements are more like aimless wriggling, vary constantly, and affect different muscles. Tic is more subject to the will.

Hammes observed choreiform movements in 8 out of 154 cases of *epidemic encephalitis*. Choreic and choreo-athetoid twitchings are described by Archambault as occasional sequelæ of encephalitic attacks. Differentiation of chorea from encephalitis demands familiarity with the latter's changing peculiarities in different epidemics. It has no rheumatic or cardiac association; its transient and migratory pareses and its epidemic character should be of value in making the differential diagnosis.

Severely paretic examples of Sydenham's chorea can readily be confused with *acute anterior poliomyelitis*, especially during an epidemic. Choreic movements, if detected, make the diagnosis.

It cannot be said dogmatically that *senile chorea* is properly Sydenham's. Probably the great majority of cases are not, but are related to such gross organic lesions of the brain as occur in posthemiplegic chorea and Huntington's chorea. The movements of chorea are less active in senility than in childhood.

Posthemiplegic hemichorea may be confined to an arm or leg, and depends on the cerebral process that gave rise to the hemiplegia. *Little's disease*, cerebral hemiplegia, or diplegia may be associated with some choreiform movements. Its appearance at or shortly after birth is evidence that the condition is not Sydenham's chorea, and its typical spasticity and pronounced pyramidal tract signs are characteristic. *Congenital athetosis* is marked by similarly distinguishing cerebral signs. Each individual movement of athetosis begins and develops more slowly than in chorea.

Huntington's chorea can be distinguished by the heredity, the past history, the onset in late adult life, its chronicity, the greater breadth of movements, and the dementia.

Paramyclonus multiplex is practically always bilateral, and is seen in the sudden contraction of a single muscle or muscle bundle, with fibrillary twitching. Muscles are not involved in groups. The face, so generally affected in Sydenham's chorea, practically always escapes.

Friedreich's ataxia occasionally suggests chorea by producing abrupt movements in the face and extremities. The gait is, however, more staggering and reeling, and the subsequent course makes the diagnosis certain.

Dystonia musculorum deformans in its early stages has been confused with chorea. The twitching is more athetoid, and the pathognomonic torsion spasm, as well as the evolution, differentiates it.

Various *intoxications* and *multiple sclerosis*, with rhythmic tremblings, are in rare instances confused with chorea.

Treatment.—Absolute rest in bed for three to six weeks is the best treatment for most cases and the necessary treatment for the more severe conditions. Relative rest is of value in proportion to the degree of loss of sensory stimulation. Application of a cold pack once or twice daily is one of the best sedative measures. Hyoscin hydrobromid, in 1/150- to 1/100-grain doses, is valuable for subcutaneous administration in severe conditions and may be given by mouth for longer periods as a sedative in milder conditions. Chloral, 5 to 10 grains three or four times a day, with bromid in equal or greater amount, is a suitable drug to relieve great motor restlessness, excitement, and insomnia. Morphin and even chloroform inhalations may be needed to control intense paroxysms.

Several lumbar punctures with moderate drainage of fluid apparently prove beneficial during the rest treatment, especially when the disease is severe.

The classical treatment of chorea is the administration of Fowler's solution in short courses, beginning with 1 minim three times daily after meals, and increasing by 1 to 3 minims daily to tolerance. Such treatment, beginning with a larger initial dose, may be repeated several times. The signs of arsenical toxicity are puffiness under the eyes and gastro-intestinal symptoms, particularly diarrhea. Overlong treatment with this solution may cause toxic neuritis. Intravenous medication with arsenic derivatives is much favored today. Jelliffe recommends four successive weekly injections of arsphenamin in doses appropriate to the age of the patient. Marinesco gives several doses of 0.15 to 0.3 gm. of neo-arsphenamin intravenously daily or every other day. Intramuscular injection of sulpharsphenamin is still experimental, but may be tried.

The use of salicylates in large doses reaching tolerance has been recommended on good authority, and undoubtedly has often been successful. Another form of treatment, not yet standardized or generally accepted, is the subcutaneous injection of foreign protein or of the patient's own serum.

Carious teeth and infected tonsils, which constitute especially dangerous foci of infection, should be carefully examined and treated. Particular attention is due the heart, which is often the seat of endocarditis. Dilatation is a common abnormality. Direct therapy is necessary for whatever cardiac complications are present.

In convalescence, anemia and malnutrition can be combated by administration of cod-liver oil with malt, iron, and arsenic tonics. Ample food of a simple and well-balanced type, usually including a good deal of milk, should be ordered. Massage and passive movements are often beneficial. Electricity should be avoided. In a survey of pediatric after-care, Irving found that supervised activity did not lengthen the course of the disease, and that choreic convalescence is not hindered by association with other patients. Outdoor exercise, work, and play rather favored complete return to good health.

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SPASM, TIC, AND TORTICOLLIS

A spasm is a sudden involuntary rigid contraction due to muscular action. When persistent it is called tonic; when characterized by alternate contraction and relaxation, clonic. Spasm is usually attended by pain. It interferes with function and produces involuntary movements as well as distortion.

The type known as *reflex spasm* is evoked by some exciting stimulus such as a local lesion in the skeletal, motor, or sensory domain.

A tic is a recurrent spasmodic involuntary muscular action confined to a few muscles or muscle groups, without the presence of a peripheral irritative cause. Presumably a tic is cortical in origin.

Pain, often present with reflex spasms and even a symptom of certain tics, is the particular feature of the so-called *tic douloureux* which is, properly speaking, not a tic. It is a special type of reflex spasm of the face associated with paroxysmal facial pain of great intensity and dependent upon changes in the corresponding fifth cranial nerve. A reflex spasm may persist after the excitant is relieved. This is often true in blepharospasm, which is a clonic-tonic spasm of the orbicular palpebrarum muscle, usually beginning in some period of ocular irritation, but persisting as a habit after its subsidence.

Local hysterical spasms have no physical excitant, but are evoked by a psychic stimulus. Like a tic in this regard, they are separated from tic only somewhat arbitrarily. They are less constant in localization than a tic and are chiefly recognizable by the fact that they vary greatly in extent and degree in the same patient from time to time, and are associated with hysterically emotional, even convulsive, states. Disappearance of a spasm during sleep is not a sign that it is necessarily hysterical. Reflex spasms

and other organic spasms may be absent then also. Peristence of the spasm during sleep, however, is sure evidence that the condition is organic in nature and not hysterical.

A so-called *habit-spasm* is a persistently repeated involuntary clonic motion which, when sufficiently severe, is a tic. A very common type is the ordinary facial tic which produces a frown, a sidewise twitch of the mouth, or similar movement.

A *tic* is radically different from the movement in chorea since in the latter condition no one movement is repeated regularly again and again. Tics, while invariably psychogenic, have in individual cases an accompanying physical reflex element. In such instances, the boundary lines between these types of spasms all but disappear. It is conspicuous that tics occur in patients prone to psychasthenic reactions, and that those sometimes associated with acute psychasthenia are transient. Such tics can best be ignored in therapy, for they disappear when the psychasthenia is treated.

A type of spasm which is being more and more widely recognized depends on lesions in the midbrain and basal ganglia. It can be labelled *central spasm*. Unusual states of clonus with clonic or tonic movements must all be studied with such changes in mind. The prevalence of encephalitis has made this clear. In individual cases, it is necessary to look for other signs of previous encephalitis, or to consider whether infection or trauma of any kind has altered the integrity of these basic centers of motor control.

Torticollis is a tonic or tonic-clonic spasm of the neck muscles which causes wry-neck. It is usually considered a distinct disease, but is, more correctly, one of the types of spasm just described. The torticollis which accompanies cervical Pott's disease is a reflex spasm which is increased in later stages by the mechanical misalignment. Another reflex torticollis is the so-called labyrinthine type. This follows irritation of the semicircular canals of one side. At times torticollis is a habit phenomenon, really an example of tic. Still other types are central in origin; that is, they follow organic changes in the region of the basal ganglia.

Treatment.—The treatment appropriate for torticollis and for all other local spasms depends entirely on their etiology. It varies, therefore, from the cure of tuberculous spondylitis to the removal of psychic abnormalities. Spasm of central origin may be helped by midbrain sedatives such as hyoscin. Torticollis may occasionally be improved by surgical division of the spinal accessory nerve or by division of the combined trunks of the three upper cervical segments.

THOMAS K. DAVIS.

DYSTONIA MUSCULORUM

(*Tortipelvis*)

"*Dystonia*," as a general term, indicates a state of abnormal tonus of muscle, but "*dystonia musculorum*" describes a clinical entity. It is a rare chronic disease characterized by irregular, involuntary, clonic contortions of

the trunk and proximal muscles of the extremities and characterized, as well, by constantly shifting tonus in the affected muscles. The face is usually not involved.

The disease affects both sexes and usually begins near the end of the first decade of life. It results from certain progressive lesions in the lenticular nucleus. While it is possible to conclude that the changes are degenerative, their exact cause is not yet clear.

While the patient is sitting quietly or lying down the symptoms are almost entirely in abeyance, but they begin as soon as voluntary movements are initiated. The abnormality is most conspicuous in walking and the contortions bend the body and twist it forward and sideways in a most bizarre manner. They seem focused at the pelvis.

The muscles remain free from trophic changes. The normal reflexes persist, abnormal responses referable to lesions of the pyramidal tract are absent, and sensation is unimpaired. The mentality remains normal.

No therapy has produced important or lasting benefit.

Thomas K. Davis.

CONVULSIVE STATES

Convulsive states, convulsions, or fits comprise those disturbances of the motor system that are characterized by sudden, violent, more or less widely distributed discharges of muscular energy, usually preceded by loss of consciousness and followed by a period of profound relaxation, exhaustion, or stupor. They are observed in all periods of life from infancy to old age and represent a clinical syndrome caused by many different etiological factors. In fact, as Hartman and Di Gaspero point out, they may be a symptom of birth trauma, congenital cerebral defect, hypertrophy of the brain, mechanical or emotional traumatism, spasmophilia, tetany, severe burns, meningitis, reflex irritation, gastro-intestinal intoxication, intestinal parasites, diseases of the heart and kidneys, cerebral arteriosclerosis, eclampsia, abscess, encephalitis, syphilis of the brain, chronic alcoholism, saturnism, tumor, hemorrhage, emboli, and other conditions.

Considering the great variability in the life periods and the multiplicity of causes under which convulsive seizures occur, it is to be expected that they will differ greatly in pattern, in rhythm, and in severity, according to the age of the individual, his constitution, and the etiological agent. A single seizure preceding the difficult eruption of a tooth in an otherwise strong, healthy baby appears to have little in common with a prolonged series in an unhealthy rachitic child suffering from a severe gastro-intestinal disorder. The slight attack of petit mal bears hardly any resemblance to grand mal or to uremic convulsions, but in each instance the same mechanism is operative and the essential elements of the fit are present.

A typical convulsive seizure consists of certain elements that are invariably constant, namely, sudden loss of consciousness, muscular spasms, and

severe exhaustion after the muscular activity subsides. As we shall see later on, these three elements are capable of variations in intensity and duration and may be augmented by many other features. Thus, the sudden loss of consciousness may be preceded by a sharp cry, great restlessness, and hyperirritability; the spasms may be tonic or clonic, or both; the period of exhaustion may be represented merely by a feeling of mild lassitude or may consist of a profound stupor lasting a few moments or many hours. Disturbances of circulation and respiration always accompany severe convulsions no matter what the type may be, although one may frequently miss them in some milder forms.

The exact mechanism by which convulsions are produced is still the subject of dispute, and is a long way from complete elucidation. A great mass of experimental and clinical data has been accumulated in the attempt to solve the problem, but the mystery of the process is still baffling. Experimental evidence is at hand in sufficient quantity to demonstrate beyond doubt that various parts of the brain cortex, midbrain, and medulla can be isolated, and stimulated either electrically or pharmacologically, so as to produce clonic spasms of the facial muscles and the extremities.

It was demonstrated years ago that temporary interference with the blood supply of the brain would produce convulsions in experimental animals. More recently Leonard Hill compressed his own carotid sufficiently long to produce paresthesias and clonic spasms in the opposite extremities. The participation of the cerebrovascular apparatus has been further demonstrated in man by Foster Kennedy and Hartwell, who observed a convulsive seizure during a cranial operation under local anesthesia, and agree that during the initial stage there is a sudden blanching of the cortex followed suddenly by terrific engorgement of the cortex and all its vessels, and by a rapid rise of intracranial pressure. The blanching was coincident with the tonic stage, and the period of engorgement corresponded to the clonic phase. This most interesting observation furnishes strong corroborative evidence for the theory that all severe convulsions start in the cerebrovascular apparatus, but unfortunately gives no clue to the factors causing the vascular cramps. The experiments of Elsberg and Stookey have demonstrated that something more than mere loss of blood-plasma is necessary to cause discharge of all energy. In the course of a series of elaborate experiments, they were able to deprive the brains of cats of practically the entire blood-supply and substitute Ringer-Locke solution. As long as the substitution was made with sufficient care no convulsions occurred during the procedure, and the experimental convulsions could be produced as before. A point of great significance is that in this experiment the brain was not abruptly deprived of the agent required for removing cellular waste products. These observers were also able to demonstrate that diminution of the alkalinity of the blood by lactic acid did not affect the production of artificial convulsions.

Sachs believes that this observation directly controverts the opinion of Cuneo, who studied a large group of epileptics in whom he found starch intolerance and highly acid stools. Cuneo believes that this group presents certain abnormalities of the alkali-forming function of the liver and small intestines, whereby the acid organic salts which should be transformed into sodium carbonate do not undergo this change. Rather they enter the circulation as such, and cause division, under certain conditions,

of the nucleohiston element into nucleinic acid and proteoses. These substances remain free and exhibit their convulsive action. Cuneo adduces a certain amount of therapeutic evidence to justify his theory through the fact that most of the members of this group were greatly improved by a restriction of the carbohydrate content of the food intake, and by the injection of an alkaline solution containing nucleinic acid. The reason for the latter lay in the hope that the nucleinic acid would combine with the proteoses and render them innocuous (quoted from Osnato).

Hartman, Di Gaspero, Di Crinis, H. Pfeiffer, and others have made careful biochemical studies of patients suffering from convulsive seizures, principally epilepsy, and have contributed many interesting observations that have greatly augmented our knowledge of the humoral pathology of these states. Perhaps the most important feature of this work has been to prove the similarity of convulsions to the disease states caused by toxic split-protein products. Toxicity of the urine, rise in the antiproteolytic serum titer, and rise and fall of the leukocyte count occur in severe convulsive states just as in anaphylaxis, severe burns, retention uremia, etc. There is, however, little or no evidence to show that the substances found in the blood and urine possess actual causative properties. On the contrary, they are undoubtedly toxic by-products of the convulsions, or disturbances in the protein metabolism that parallel the seizure.

The chemical similarity of some of the amino-acids to the secretions of the ductless glands has led endocrinologists to search the elements of the latter for an explanation of the phenomenon, but as yet the matter remains largely in the domain of speculation. To be sure status thymicolymphaticus is frequently observed in the convulsions of childhood or adolescence, and a large group of epileptics have pituitary or thyroid disturbances, but thus far nothing more than a remarkably constant participation of these types in the general biological disturbances of the individual has been established.

The convulsions of infancy, likewise present the same baffling problems. For a long time explanation was sought in the belief that the inhibitory powers of the cortex were incapable of functioning properly, and therefore allowed an abnormal reflex irritability of the lower centers to release massive motor stimuli. In recent years, however, the development of the pathology and symptomology of tetany has made it possible to separate a group of infantile convulsions, in which so many of the characteristics of this condition of excitability of peripheral nerves and muscles are present, that there is every reason to believe they are members of the same group of disorders of calcium metabolism and possibly disturbed function of the parathyroids.

"Spasmophilia," or the "spasmophile diathesis," is the term used to designate this group, which includes laryngismus stridulus, eclampsia infantorum, and tetany. It serves admirably the purpose of correlating allied motor phenomena and metabolic disturbances, but, as Sachs rightly insists, it describes conditions, but does not explain them. Whether the marked disturbances of the nervous system are caused by alkalosis and the diminished calcium ion content of the blood, or whether they are caused by the presence of guanidin and methylguanidin circulating in the blood, is still uncertain.

Freudenberg and P. Gyorgy, in their studies on tetany and alkalosis,

started from the biological experiments of Trendelenburg, Soibel, and Van Paassen, in which the ionizing relation of blood and tissue sera were emphasized, and the diminished calcium ion content in the blood of parathyroidectomized animals was demonstrated, and established the physiochemical diminution of the calcium ion content in the blood in tetany. Paton and Findlay believe that the symptoms of tetany are caused by guanidin and methylguanidin intoxication, because they have been able to recover these substances in increased amounts from parathyroidectomized dogs as well as from children suffering from tetany; they have been able to produce tetanic symptoms by the administration of these substances; and they have been able to produce these symptoms in frogs treated with the serum of parathyroidectomized dogs.

Barker, after remarking that the facts and ideas on this subject are like a pack of scattered cards that represent mere gropings toward a satisfactory explanation, summarizes the situation as follows: "Certain it is that the effect (of the tetany poison) is exerted directly upon the neural mechanisms themselves and not directly upon the muscles innervated by the motor nerves. Furthermore, the change produced in the nervous system is not inflammatory in character, nor can it be merely a circulatory disturbance; it is probably of a toxic degenerative nature."

Experimental evidence, while valuable for the purpose of establishing principles or laws for anatomy or physiology, must always be accepted with a certain amount of reserve in pathology, except possibly in acute toxic or infectious diseases. This is particularly true as regards experimental convulsions, because of the great difference in vascular supply, cerebral elements, etc. In the case of cerebral anemia, for example, the experimental evidence shows that while lack of blood will cause convulsions, these do not occur until an appreciable interval of time has elapsed (ten minutes to several hours). In man, on the other hand, compression of one carotid only may be followed by evidences of irritation of the sensory motor cortex, in the form of well-patterned paresthesias and clonic contraction of the opposite side. The same consideration applies also when toxic convulsing agents are introduced into the circulation of experimental animals, since there is no convincing evidence to indicate exactly which neural structures are affected by these agents, nor how they act. Thus far one may be sure that a convulsion produced artificially in the cat by either method is not at all the same thing as the sudden lightning-like attack that strikes an individual out of an apparently normal state of well-being, and sends him writhing on the ground in a grand-mal seizure.

Before the present-day inclination to regard convulsions as the expression of a pathological condition caused by many different etiological factors, they were thought of in terms of clinical entities and classified as eclampsia infantum, eclampsia of the puerperium, and the epilepsias. A properly elastic classification is always helpful if it serves the purpose of separating these conditions into allied groups that have several features in common. It is rather necessary also, as approach to the case is invariably clinical, even though we may pass immediately to the morbid anatomy and base our therapy upon it. For this reason and for convenience' sake, the clinical features of convulsive states will be considered according to the following groups.

ECLAMPSIA INFANTUM

(*Spasmophilia*)

Generalized convulsions appear with greater frequency in early childhood and infancy than in any other period of life. They exhibit practically the same elements common to all convulsive seizures, and, as far as one can say, are released through the same mechanism. Most authors admit the theory that the cortical centers do not develop their inhibiting functions until after the eighteenth month. Before this the lower centers are in full control and the reflex irritability is correspondingly greater. The greater susceptibility of young infants to convulsions is thus explained, as well as the reason why otherwise healthy infants often suffer from convulsions due to apparently unimportant causes.

Mere reflex irritability or physiological spasmophilia, as Soltman and Oppenheim term it, is applicable to a limited group only, whereas there is a constantly increasing tendency to correlate spasmophilic with other disease states that are themselves closely related. The investigations of recent years, both in this country and Europe, have clearly demonstrated many common features of both tetany and spasmophilia and their close association with rachitis. Indeed, tetany is at present considered, with laryngismus stridulus, as part of the spasmophile diathesis in which convulsions may occur, together with the other two conditions. Thiemich, however, is quite justified in his opinion that only those cases that exhibit one or more of the signs of tetany belong to the pathological spasmophile diathesis, and one should be able to elicit the phenomena in the interval between seizures. First, in the order of frequency of occurrence, come Chvostek's sign of increased excitability of the facial nerve to mechanical stimulation, and Erb's sign of increased excitability of the nerve trunks to galvanic stimulation. In order to establish the latter, K O C must occur with a current under 5 M A, and A O C must be greater than A C C. Trousseau's sign, Pool's leg phenomenon, the carpopedal spasm, and arthrogryposis are less constant and denote a greater intensity of the condition.

There are, without doubt, conditions other than spasmophile diathesis where an abnormal tendency to convulsions is encountered. For lack of finer distinctions and because of the hereditary, congenital, and other constitutional factors that combine to predispose the individual to convulsions, we group them under the term "neuropathic diathesis."

Etiology.—Convulsions of early childhood and infancy frequently result from reflex irritability caused by simple mechanical factors, among which difficult dentition, intestinal parasites, and a stomach full of indigestible food are the most common factors. The capacity of these conditions to produce convulsions has often been doubted, and in the case of dentition it is asserted that an underlying rachitis is the real cause. However, most authors agree that both of these latter conditions may act in a purely mechanical way. Injuries and psychic trauma (fright, etc.) may also be considered as mechanical agents. The onset of any one of the exanthemata may be proclaimed by a seizure, or it may occur during the course of a middle-ear infection, a severe reaction to vaccination, or during the onset of pneumonia, poliomyelitis, and epidemic encephalitis. A single convulsion or a mild serial attack during the onset of one of these diseases has no grave significance, and has been aptly compared to the initial chill of adults.

Severe exhaustion resulting from gastro-intestinal catarrh, chronic diarrhea, loss of blood, or any other disease may excite eclampsia. The relationship of rachitis to spasmophilia has been mentioned elsewhere, but it is still commonly classed with scrofula as one of the predisposing causes of convulsions.

Poisons circulating in the blood-stream may cause convulsions. The toxins of uremia and ptomains, alcohol, lead, opium, and santonin have been described in this connection, but are infrequently encountered. Uremic convulsions are occasionally seen in the newborn child of a mother suffering from uremic eclampsia.

Organic lesions of the brain cause convulsions. Abscess, tumor, hydrocephalus, and injuries to the brain at birth may remain unsuspected until betrayed by a convulsive seizure. Meningitis or encephalitis may also announce themselves in this manner, and in the very early stages it is often difficult to determine whether the seizure is a result of direct action of the pathological process or the indirect effect of reflex irritation.

Heredity plays an important part in the constitutional make-up of the individual who exhibits certain types of convulsions. Alcohol, chronic lead poisoning, psychoses, etc., in the parents predispose the children to neuropathic diathesis, if nothing more. Certain districts in France, where chronic saturnism is prevalent, furnish a large proportion of children with rachitis and spasmophilic diathesis among other abnormalities. Children of alcoholic parents are prone to develop epilepsy, and although it may still be undetermined whether a psychopathic constitution is transmitted or whether alcohol has the capacity to affect germ plasm, the fact remains that alcoholism occurs in 25.89 per cent. of the antecedents of epileptics, according to Barrett.

Davenport and Weeks have also demonstrated that epilepsy, in common with feeble-mindedness, is transmitted in a recessive manner, inasmuch as 30 per cent. of the offspring of parents who have nervous disorders are epileptic or feeble-minded. Healthy parents who beget epileptic children have near relatives who are abnormal.

Symptoms.—The convulsions possess the essential characteristics of an epileptic seizure, although there are several individual features which help to distinguish them from the latter. The different phases are usually less clearly defined. The entire attack may be limited to one or two phases only. The muscular spasms alone may constitute the seizure without loss of consciousness or the initial cry. In fact, Ausset is inclined to believe that the absence of the initial cry is of diagnostic value in the differentiation from a grand-mal seizure. Tonic contraction and the decerebrate posture, the fingers clenched around the thumb, the arms and legs extended, head drawn back or to the side, may alone constitute the motor signs, or tonic may be succeeded by clonic contractions involving the entire skeletal musculature or limited to a few muscles. Frequently clonic contractions alone are seen without preceding tonic spasms, or the typical order may be reversed and tonic rigidity follow clonic elements. When no loss of consciousness occurs, only clonic elements are usually seen, and the attack may bear a certain resemblance to the myoclonias that sometimes occur in so-called idiopathic epilepsy. Sachs lays particular emphasis on the significance of partial convulsions limited to a single limb or a group of

muscles, and points out that they usually represent the early signs of organic lesion of the brain.

A careful search for these signs in the history of every convulsion is, therefore, of the utmost importance, and should not be overlooked. Series of attacks and a tendency to rapid alternation of the tonic and clonic elements are seen with much greater frequency in early childhood and infancy than at any other period. This occurrence in itself carries no particularly sinister significance, since it is usually a sign of extreme reflex irritability of the individual, and not necessarily one of grave disease.

Prognosis.—The elements of danger attending the convulsions are to be found during the initial respiratory phase, when a prolonged spasm of the muscles of respiration may provoke serious cyanosis, asphyxia, and engorgement of the cerebral vessels. A fatal termination of permanent injury to the brain can occur before one is able to relieve the cramp. Occasionally head injuries from falls during the onset, or striking against the bed during the clonic stage, may lead to serious consequences.

Serial attacks lasting for more than twelve hours and accompanied by persistent coma are usually signs of grave disorder, inflammatory or otherwise, and frequently lay the foundation for serious organic lesions, the effects of which may become apparent in adult life.

The exact significance of convulsive seizure is often a matter of great uncertainty, which sometimes only time will decide for us. It may be repeated for a few times, or for a few weeks, and then disappear never to return. One single attack may provoke structural changes in the nervous system from which either a fatal termination or at least permanent defects and deformities result.

Convulsions of the newborn are always to be regarded as serious, because they invariably represent either a maternal intoxication acquired during fetal life, or birth traumas caused by pressure on the soft cranial bones. In either event, the consequences are grave, since the individual is likely to be burdened with an organic disease or at least an unstable nervous system for the rest of his life.

The relationship of infantile convulsions to epilepsy is still the subject of considerable discussion, and although it has occupied the attention of many different authors, opinions concerning this question are far from agreement. Oppenheim, Nonne, Heubner, and Asshaffenburg are convinced that infantile convulsions are often the early evidences of later epilepsy. Thiemich, on the contrary, was able to observe his eclampsia cases until about the twelfth year, and found that although two-thirds of the total number of cases exhibited definite evidences of nervous disorders, feeble-mindedness, stammering, nervous instability, etc., not one case of epilepsy could be found. While this study is extremely interesting, it is somewhat unconvincing because of the relatively short time he was able to observe them. Furthermore, it would be surprising if among so many children with such serious sequella as feeble-mindedness and instability of various types, none should develop epilepsy in adolescence or later on.

Patrick and Levy have also studied the question with great thoroughness. They are of the opinion that convulsions occurring between the eleventh and thirteenth months are usually harmless, but when they occur before the sixth month or after the eighteenth month they are more apt to be forerunners of epilepsy. About 20 per cent. gave a history of early

convulsions in an epileptic group, whereas only 4 per cent. of an unselected group gave a similar history.

Serial attacks, especially if followed by a period of stupor lasting more than an hour, are always to be regarded with concern. If no exciting factor is found, there is grave danger that the first evidence of epilepsy is at hand. On the other hand, even though a so-called reflex cause be present, it is likely that the foundation for future epileptic seizures or disabling neuroses is laid down at this time.

Clonic contractions limited to one side of the body, to one limb or part of it, without loss of consciousness, no matter how innocent they appear, should always be the signal for an exhaustive search for evidences of underlying organic lesion of the brain. Signs of a beginning brain tumor may be detected at once if this warning be heeded; but, even though no symptom other than the fit itself be present, we are at least warned of the danger and can inaugurate an extended period of observation. Occasionally no signs develop, and years later that which was once so harmless in appearance gradually progresses through the stages of loss of consciousness, tonic rigidity, etc., and a typical grand mal ensues for which surgical exploration can find no cause.

Treatment.—Every plan of treatment should include the management of the seizure, the prevention of its immediate recurrence, and the removal of the cause. In many instances the actual seizure is short lived, and by the time the doctor arrives the convulsive movements have ceased. If this is not the case, he will find at least that the ordinary household remedies—hot mustard baths, mustard poultices to the spine, abdomen, and feet, etc.—have already been applied and possibly an enema given. One is, therefore, usually in a position to estimate how serious the convulsion is, and is able to choose his remedies with better understanding. If the condition is serious, without signs of recession, and asphyxia becomes imminent, chloroform should be resorted to immediately. It is harmless if carefully administered, and can be given until the movements subside. A few drops only will usually enable us to produce narcosis sufficient to control the spasms. If the convulsion is less severe, a small dose of morphin or codein may be given, or chloral by rectum. It should be borne in mind, however, that our energies should be directed toward relieving the fit as soon as we can, because the possibilities of future harm as a result of prolonged cerebral congestion are very grave. Sachs warns emphatically against the use of counterirritants and emetics. He insists that counterirritants are of no value, that they cause the loss of valuable time, and possibly increase the existing hyperirritability. The use of emetics he considers dangerous, because the vomiting adds to the cerebral congestion that already prevails.

After the recession of the convulsive stage, morphin, codein, bromids, chloral, or luminol are most highly recommended and best adapted to prevent its immediate recurrence. Even moderately severe attacks are likely to recur at any time during the next few days unless prevented by some of these measures. Chloral or bromids are more readily administered by rectum, and are best suited to the period when consciousness returns and the general irritability becomes enhanced. As this state moderates, a change to luminol in small doses is recommended as the best measure of control. This drug can be given for a relatively long time without harmful effects. Rest and quiet are also most essential during this period.

During the stage of recovery a thorough search for the causal factors should be instituted, and, once they are found, the proper therapeutic measures should be started as soon as may be practical. All agents acting as reflex irritants, worms, undigested food, etc., should be removed, erupting teeth should be helped if possible in their passage through the bone, and the proper care of the infectious diseases should be inaugurated. In other words, after relieving a symptom which is often full of baneful possibilities, we must turn to the various departments of general pathology for guidance in the further management of the case.

PUERPERAL ECLAMPSIA

(*Eclampsia Gravidarum*)

Convulsions occurring during the terminal stages of pregnancy, during the actual labor, or in the postpartum period are especially sinister not only because of possible disastrous consequences to the child but also because the life of the mother is frequently at stake. In no other department of special pathology does the convulsion bear the same relationship to the life of the individual; for until the advent of more successful principles of therapy, 25 per cent. of all such cases may terminate fatally.

Etiology.—The pathogenesis of eclampsia gravidarum has always been one of the grave problems of obstetrics and is still a long way from elucidation. The constant appearance of albumin, casts and blood in the urine, the frequency of albuminuric retinitis and other nephritic signs lead one to consider the kidneys at fault. Years ago this was thought to be the result of mechanical pressure on the ureters; but, later on, this idea gave way to the theory of actual kidney disease, which rendered these organs incapable of eliminating certain toxic nitrogenous elements from the blood-stream. The numerous instances of convulsions with little or no albumin or cellular elements of the kidneys, on the one hand, and, on the other, the equally numerous instances of women suffering from severe renal disease, who successfully endure pregnancy without convulsions, furnish sufficiently valid objections to this theory, however, and we find still further evidence in the remarkably similar metabolic changes which occur in pernicious vomiting, eclampsia, and acute yellow atrophy of the liver.

In both France and Germany attempts have been made, from time to time, to place eclampsia in the list of infectious diseases. Delore, and later Blanc, found a micro-organism in the blood and tissue of women suffering from eclampsia, and more recently Schraiber, Haegle, and others have described a specific bacillus. This organism, however, was demonstrated to be *Bacillus proteus vulgaris*, which possesses no such specific qualities.

The theory of placental participation has a greater following both in this country and abroad. The first idea was that through improper function fetal waste products were permitted access to the maternal blood. A further elaboration of this notion resulted in the theory that toxic albuminous products elaborated in the placenta found their way to the maternal blood-stream, because of imperfect formation of destructive protective substances.

The discovery of a specific enzyme in the placenta led Hofbauer to believe that these structures escaped into the maternal blood and there set up a process of protein destruction that overwhelmed the host.

The general trend of opinion appears to be toward a combination of many factors. Ewing, for example, in commenting on the similar features of pernicious vomiting, acute yellow atrophy, and eclampsia, expresses the belief that there may be an additional renal factor which accounts for the convulsive elements of the latter. F. S. Hammet believes that the cause arises from a decrease or perversion, or both, of the intermediary metabolic function of the placenta accompanied by an increased permeability of the endothelium covering the villi projecting into the maternal sinuses; the combined effect of this increased permeability and decreased detoxicating activity contrives to flood the maternal organism with incompletely hydrolized by-products of fetal metabolism. This apparently places an overload on the kidneys and liver which they are unable to meet. A subsequent toxemia results.

The theories of intoxication do not suffice for other students of the subject. Zuntz and Blumreich were able to demonstrate that certain motor nerve-centers of pregnant animals possess an increased sensitiveness to creatin, and were led by this to postulate a theory of a specific hypersensitiveness of these centers in certain women, which predisposes them to convulsive seizures.

Increased excitability of vasomotor centers and edema of the brain caused by a pathological reflex process emanating from the uterus have also been advocated as the cause of the condition, but the evidence in support of these theories is still inconclusive, especially as regards the latter, since there is little to show that we are not dealing with an effect rather than with a causal factor.

Morbid Anatomy.—Extensive changes are found in the liver, kidneys, and other viscera. They consist in multiple thrombi, cloudy swelling, and granular degeneration of the parenchyma. Emboli containing granular cells of the placenta were found distributed throughout the body by Schmorl; and cerebral hemorrhages or intense edema of the brain have also been found, but it is generally conceded that all these changes are the effects of the profound intoxication, or the mechanical results of the convulsion.

It thus becomes apparent, after consideration of the evidence at hand, that although a great deal has been learned concerning the metabolic changes that follow eclampsia gravidarum, there is at present no clear undisputed conception of the actual process by which these morbid conditions are produced.

Symptoms.—The actual seizure is essentially the same as a severe epileptic attack and differs chiefly in the severity, the tendency to series, and the general inclination to prolong the tonic phase. In severe cases the cyanosis, the disturbances of respiratory rhythm and pulmonary circulation, and the stupor are intense. The entire picture is in reality one of status epilepticus. The temperature often rises to an alarming degree.

The attack may be preceded by signs of general toxemia, consisting of albuminuria, edema of the face and extremities, headache, dizziness, scotoma, or hypersensitiveness to pressure. Delirium, usually of the occupation muttering type, or great restlessness is occasionally seen during the intervals between the attacks, and less frequently after they have subsided: temporary blindness, paresis of the extremities, or puerperal mania may complete the picture.

When death terminates the struggle it occurs from cerebral hemorrhage, split protein intoxication, sepsis, or pulmonary fat emboli (Nonne).

Treatment.—The principles governing therapy are quite similar to those of infantile eclampsia: prompt control of the seizure and reduction of the hyperirritability of the neural centers, elimination or neutralization of the toxic substances circulating in the blood-stream, and the rapid induction of labor.

The convulsion is best controlled by chloroform narcosis, which should be maintained as long as there are indications that irritation of the nerve-centers persists. After this has been accomplished, a further diminution of cerebral irritability should be sought in the administration of fairly large doses of morphin and chloral hydrate. Even while these measures are in operation, steps should be taken to promote elimination through all physiological channels. Vigorous catharsis by means of high rectal enemata, diuresis by colon irrigation with saline solution or sodium bicarbonate, the Murphy drip, or hypodermoclysis; diaphoresis from hot moist packs should be inaugurated as soon as conditions will permit. If the individual is robust and plethoric, one can employ venupuncture with subsequent removal of 250 to 500 c.c. of blood to advantage.

The indications which make it advisable to empty the uterus depend on the severity of the intoxication and the condition of the patient. This procedure, whether accomplished by artificial dilatation of the cervix and induction of labor or by Cesarean section, is always dangerous and should only be employed where there is no doubt of its wisdom. Indeed, there are many who doubt the value of any interference at all in this direction.

Edwin G. Zabriskie.

EPILEPSY

Modern pathology has taught us that a clinical phenomenon called epilepsy, and formerly considered to be a separate entity, is, in reality, in most instances a syndrome, which may result from any one of an infinite variety of etiological factors. The tendency at present is more and more to limit the use of the term, and to consider the convulsion in the light of our more intimate knowledge of the underlying pathology. We have thus been provided with a more intelligent method of therapeutic attack and, furthermore, we are able to avoid the use of a term which *per se* creates a reaction of terror and consternation to whomsoever it is applied.

A concept which for centuries has been made to designate so dramatic a dénouement must inevitably die hard, and, therefore, we find it still in use, although its application is greatly restricted.

There are still many authors who believe that there is a class of cases to which the term may rightly be applied. These constitute a rather large group of so-called idiopathic or essential epileptics, who exhibit none of the afore-mentioned etiological determinants, unless an almost invariably con-

stant neuropathic constitution is to be considered in this light. Feré prefers to call them, and with every right, epilepsy without known cause. Sachs believes that epilepsy is a condition characterized by convulsions without a special assignable cause for each seizure, and by a tendency to mental deterioration. Binswanger also believes that there is a group answerable to no known structural cause which he prefers to call dynamic-constitutional. Redlich, however, long ago discarded the concept and insists that even in this group, which he calls chronic epilepsy, the seizures are based on some anatomical process which may be either a pathological lesion or a congenital defect.

Symptoms.—The classic type of epileptic seizure begins with a rapidly progressive or extremely sudden loss of consciousness. There may be no warning at all, but a sudden pitch forward or backward, with complete muscular relaxation and complete inhibition of all self-protective instinct. In more than 50 per cent. of the cases the loss of consciousness is preceded by the sinister outcry, the nature of which is still somewhat obscure.

During the initial stage of relaxation, or more often preceding it, there is intense pallor of the face and blanching of the hands. The tonic phase which closely follows is characterized by general muscular rigidity of the decerebrate type. Usually respiration ceases, the skin resumes its normal color, and progresses into various stages of cyanosis. It is during this stage that the tongue is usually bitten, because of the intense cramp of the masseter muscles. The tonic phase relaxes in a disorderly manner with no regulation of time or sequence. There may be a sudden general relaxation or a partial release of one side, so that one sees clonic spasms on one side of the body and tonic rigidity on the other. The clonic phase then becomes general, and there follows a period where the individual is affected with rhythmic violent jerks distributed over the entire body. Sometimes they begin in the legs and spread upward, or they may first appear in the extremity in which sensory auræ preceded the attack. Coughing, grunting, or stertorous sounds are heard, foam, clear or blood-tinged, appears on the lips, the bladder or rectum may be emptied with great force, and occasionally seminal ejaculations occur. Petechial hemorrhages in all parts of the body have been seen during this stage, and several cases of rupture of the heart have been reported.

The clonic phase lasts much longer than the tonic, usually three to five minutes, and then gradually subsides, the cyanosis slowly fades, and the patient lapses into a state of exhaustion or complete stupor.

During the convulsive stage, certain definite cardiovascular changes appear which have been admirably described by Pollock and Treadway. The pulse becomes rapid, small, often thready; diastolic arhythmia is found before, during, and after the convulsions. The blood-pressure, after a sudden rise, drops rapidly during apnea and remains low during the fit. The pupils are at first contracted, but dilate soon after and are almost invariably immobile to light. The retinal vessels, at first contracted, dilate, and become greatly congested. The deep reflexes are nearly always greatly diminished or abolished during the convulsive stage and then gradually reappear during the stupor. The period of stupor may be entirely wanting and the patient may emerge from the fit fully conscious and only mildly exhausted, but usually there is a phase of profound stupor lasting either a few moments or

many hours. It may be followed by a few automatic purposeless movements before normal sleep ensues. There is always complete amnesia of the seizure which may include quite an interval preceding the attack. On awakening, besides the feeling of fatigue, there may be intense bitemporal headache, nausea or vomiting, and more or less severe joint pains and aching muscles. The stupor, however, may be followed by a cloudy dream state, by active delirium, violent manic states, or great automatic psychomotor activity.

Instead of a single convulsion there may be a series of rapidly recurring attacks which constitute the condition known as *status epilepticus*. They are usually accompanied by a profound stupor, high temperature, rapid loss of body weight, and all the signs of an alarming intoxication. The pulse is thready, dicrotic, and often so rapid that it cannot be counted. Death usually follows cardiac dilatation or pulmonary edema. If death does not terminate the attack, the patient lapses into a coma from which he recovers very slowly.

In about 50 per cent. of all cases, according to Gowers, the convulsion is heralded by warning symptoms known as auræ. They are really the first stage of a fit whenever they occur, and are to be considered as an integral part of it. They encompass the entire sensory gamut, and are classed according to the location. Optic or auditory auræ are relatively rare and take the form of visual or auditory hallucinatory phenomena: gay colors, terrifying red sparks, or fortification scotoma, phonemes, or melodies. There are also auræ of taste or smell of something burning or extremely unpleasant; paresthesias often strictly localized in any part of the body; local cramps or pareses, automatism, impulsive acts; vasomotor auræ, *i. e.*, angiospasms, erythema fugax, or sudden sweating; psychic auræ, anxiety states, sudden outbursts of rage, euphoria or ecstatic states, illusive memory pictures, etc.

Grand mal seizures may be interlarded with atypical attacks, or either group may occur alone in one individual. Instead of a convulsion, the patient may experience merely some of the above-mentioned auræ with or without momentary loss of consciousness, or the picture may present all the essentials of the grand seizure, except that the convulsive elements are so slight that they pass unnoted. The motor components may consist of aggressive acts, dancing, springing and turning movements, ending in the usual collapse or in a psychotic state. In this category belong epilepsia procursiva, in which the individual runs blindly forward, to the side, or backward, oblivious of whatever may be in his way, or epilepsia rotatoria, *i. e.*, the running amuck of the Malay or Salaam fits.

Petit mal attacks consist in momentary loss of consciousness betrayed by the slight sway or jerks of the head, or a sudden interruption of the stream of thought. It is characterized by a great variety of motor phenomena, such as yawning, stamping, and chewing, and by sensory disturbances in the form of paresthesias, sudden blindness and scotomata. There is often sudden blanching of the skin which regains its normal color with the return of consciousness.

Psychic disturbances may occur as direct concomitants of the convulsions or as substitution phenomena. The latter type are called *equivalents* and actually replace the convulsive movements. For this reason they are considered to be part of the petit mal group. They comprise all forms

of automatism, usually exhibiting twitchings of the muscles, blinking, word perseverations, etc. One of the common forms of equivalent is that known as exhibitionism, but patients may fall into violent homicidal manic rages from which they emerge quite oblivious of what has gone on. According to Turner they are to be recognized by their occurrence in individuals suffering from grand mal attacks, and usually represent the psychic features of the attack.

Between attacks the frank epileptic is usually a constitutional psychopath of the most disagreeable sort. He fatigues easily, is hypochondriacal, quarrelsome, and subject to rapid unexplainable variations of mood. According to Clark and Scripture, about 50 per cent. exhibit a peculiar monotonous variety of speech known as the plateau type. Their abnormal personality is characterized by non-social instincts; they are gloomy, irritated by trivial incidents, suspicious, and constantly on the defensive. In spite of a great outward show, they are usually very poor in emotional qualifications and try to compensate by means of exaggerations, boasting, and fabrications of emotions they do not really feel. Hypersensitive to a marked degree, they fly into violent rages over mere trifles, take offense at the most innocent remarks, or become sulky, disagreeable, or suspicious for no reason at all. They are very rigid, and usually attempt to impose their views of life on those with whom they associate. Egocentricity is another prominent characteristic. They are self-centered, unable to grasp the viewpoint of others, and childishly uncomprehending when forced to accept the opposite view.

It has long been recognized that epileptics are prone to become alcoholic and that they are easily affected. Like manic depressives and other psychotics, they are apt to adjust their depressions through this means, and are likewise easy victims of delirium tremens.

Mental deterioration follows relentlessly in those persons who suffer for years from attacks and have not the physical or psychic vigor to successfully withstand them. It may first appear as dypsomania, poriomania, or other impulsive acts of delinquency, but before long marked irritability, rapid variation of mood, ethical depravity, pathological lying, and general dilapidation supervene, to be followed later on by a terminal dementia.

The relationship of epilepsy to infantile convulsions has been discussed elsewhere, and, although opinions are to a certain extent conflicting on this point, the preponderance of evidence appears to favor the view that convulsions in infancy, especially if severe, may predispose to epilepsy later on in life. Patrick and Levy believe that early convulsions, especially if repeated *per se*, multiply the individual's ordinary chances of epilepsy by at least 5, nor is this remarkable when one considers the chances for structural damage to an infant brain during a series of convulsive seizures.

Migraine has also been studied in this respect. Gray first called attention to the interconvertibility of epilepsy and migraine, and since then Walker, after a careful study, found that 10 per cent. of early migraine cases develop epilepsy later on. Ulrich in a similar study found the number still higher, *i. e.*, 12 per cent.

There is likewise a large group of vasomotor disturbances closely associated with epilepsy that appear in the form of sudden pallor or flushing, dizzy attacks, sudden variations of mood. outbursts of anger or depression, paroxysmal tachycardia, nausea, etc.

Binswanger claims that more than half of all epileptics present some signs of hereditary degeneracy. These may be physical or psychic. The physical stigmata appear as more or less gross anatomical variations from the normal in the form of skeletal asymmetries, deformities of feet, hands, tongue, or ears, strabismus, errors of refraction, congenital nystagmus, anisocoria, enophthalmus, and other muscular deformities. Lombroso, Besta, Redlich, and many others have remarked on the large proportion of left-handed individuals among epileptics.

More recently these anatomical variations have been studied from the endocrinopathic point of view, and attention has been called to the frequent evidence of pituitary disturbances, of which the dyspituitary type is most common. Acromegalic features are often seen, but those representing Fröhlich's syndrome are by far the most frequent. In practically all of such cases an anomaly or abnormality of the sella turcica can be demonstrated by means of radiograms.

Psychic developmental defects are present in a great majority of cases. Years ago the fact that from 15 to 20 per cent. of feeble-minded individuals develop epilepsy in later life was recorded, and since then the co-existence of psychic abnormalities in the great majority of epileptics has been firmly established. They comprise all gradations from slight deviations of personality to the most sombre forms of idiocy.

Diagnosis.—The diagnosis of epilepsy usually presents little difficulty if an accurate picture of the seizures can be obtained. The organic types may readily be recognized; the scars of a bitten tongue, or those resulting from falls or other injuries, help to visualize the profound coma of the attack. The various so-called stigmata are also of service.

Hysterical seizures have frequently been confounded with true epileptic attacks, and, unfortunately, the converse also occurs. The well-developed major hysterical attack should not be difficult to recognize, because of the striking difference in the motor phenomena. The ecstatic, erotic attitudes, the partial or complete retention of consciousness, the recall of past experiences, the portentous utterances are characteristics which the epileptic seizure does not possess. There are types much less fully developed, however, where the resemblance between the two conditions is so close that we are forced to rely for differentiation upon the so-called essential features of the fit. The fall and cry may be indistinguishable; it may be impossible to determine the degree of unconsciousness; and the motor features may assume all the characteristics of the fit. The pupillary reflexes, however, are rarely if ever lost, the tendon reflexes are always retained, while the absence of evidences of injury, *i. e.*, scars, hemorrhages, nocturnal attacks, incontinence, and amnesia, furnish positive criteria that should enable one to diagnose the doubtful hysterical seizure. Although all these signs are reported in hysteria, their occurrence is rare enough to justify a doubt of the correctness of a diagnosis of hysteria whenever they are present. Hartmann calls attention to the fact that hysterical attacks may often precede epilepsy or appear during the interparoxysmal stages, and urges that all doubtful cases be treated as epilepsy.

Treatment.—The treatment of epilepsy, just as in other forms of convulsive seizures, resolves itself into the management of the attack and the aftercare of the patient for the purpose of eradicating the attacks, diminishing their frequency, and assisting him to a better adjustment to his environment.

The management of the attack must be concerned chiefly with the prevention of injuries. Patients should be allowed to remain where they fall, and everything against which they might strike during the clonic stage should be moved away; biting of the tongue is prevented by the insertion between the teeth of some hard substance such as a spoon or lead pencil, tight clothing is loosened, and excess mucus is removed from the mouth. No attempt should be made to hasten the end of the stupor, as this is a period of repair from the exhaustion of the paroxysm; too early awakening is likely to cause headaches and persistence of the exhaustive phenomena. If the attacks are nocturnal, care should be taken to prevent falls from the bed.

Serial and status attacks may be shortened or relieved by colonic injections of ice-water; drastic cathartics, which, however, should be used with great care; applications of ice to the spine; and bromids in large doses. Chloral by rectum has been recommended, and it has been found advisable to employ morphin in combination with chloral and bromids to prevent status attacks whenever a gradual increasing frequency and severity of seizures warns us of their approach. Venesection has been highly recommended by the French because it lowers tension, and is a means of rapid elimination of the toxic properties of the blood. Clark, however, advises against its use unless it is followed by normal saline injections, except in plethoric cases. Many of these patients are already profoundly depleted, the vascular tension is low, and the intracranial pressure is also diminished. Unless the loss in volume is replaced by normal salt solution, more harm than good may result. If chloral is employed in large doses, 60 to 90 grains, care must be taken to counteract the depressive effects. Chloretone has been recommended, but is of doubtful value.

When all other remedies fail and there is sufficient warning of the approach of serious results, chloroform or ether may be used. Anesthesia should be carried to a complete surgical stage, the heart and respiration being carefully watched for signs of sudden depression, but it should never be prolonged into the stuporous stage.

The postconvulsive stupor of epilepsy requires vigorous supportive treatment; heart and lungs should be watched for possible complications; and the utmost care should be taken to prevent a return of the attacks. The free administration of alcohol, digitalis, caffein, and other stimulants has been highly recommended. If delirium is present, hyoscin 1 to 200 or small repeated doses of paraldehyd give the best results in control of motor unrest. Cool packs, friction of the skin with cold water, or warm moist packs, because of the elimination as well as the soothing effects, often suffice to restrain restlessness and thereby favor recuperation.

General Treatment.—Hygiene and diet, in the opinion of most writers, are by far the most important considerations in the general treatment. If we bear in mind that we are dealing with a disease of the entire organism in which the brain is chiefly affected, the reason for this becomes at once apparent. Not only must these patients be guarded against attacks, but they must also be protected against themselves. It is well to remember that the epileptic is a profound neuropath whose defects handicap him severely in his life reactions. He is improperly equipped to meet the ordinary demands of a normal social existence, and his capacity for adjustment to unfavorable conditions is usually limited.

Fatigue of all forms should be scrupulously avoided, since it lowers

resistance, favors irritability, increases the amount of irritating substances in the blood, and inhibits elimination. Headache, irritability, vasomotor phenomena of pallor, flushing, and unstable emotional symptoms often herald the advent of fatigue states.

Every effort must be made to place epileptic patients in an environment which will maintain as far as possible an even, unexciting, non-irritating atmosphere, in which physical as well as mental conditions are favorable. They should not be exposed to extremes of climate, irritating light effects, prolonged heat, or unfavorable atmospheric conditions. The choice of an occupation must depend largely on the capacity and inclination of the individual. In general, epileptics should not be allowed to engage in occupations demanding hard physical labor, intense concentration, or fatiguing mental work, or those which might subject them to emotional strain, worry, anxiety, or excitement.

Frequent bathing should be encouraged, and wherever possible tonic baths are advantageous. The temperature must be regulated according to the physical condition; only strong muscular patients should be subjected to extreme hot or cold water, and vasomotor stimulation in the less vigorous patients should be obtained by friction, salt rubs, massage, and similar measures.

In general, the diet should be regulated to conform with the individual need of the patient, all articles of food for which intolerance exists should be reduced, and every effort should be made to render it as bland, non-irritating, and highly nutritious as possible. The bulk should be carefully watched in order to avoid overloading; it is much more desirable to eat often than to partake of hearty meals at long intervals. All stimulants, such as alcohol, tea, and coffee should either be strictly eliminated from the diet, or used in great moderation.

Many forms of special diets have been advocated, chief among which are the salt-free diets, the purin-free diet, the lacto-vegetable diet, and the diet free from all animal proteins.

Experience has gradually demonstrated that, by itself, the salt-free diet, so warmly recommended a few years ago, has no value whatsoever, though it does serve a useful purpose, whenever it can be successfully maintained, as an aid to the administration of bromids.

The other forms of diet are similar and differ in quality only. Cuneo's carbohydrate-free diet should always be employed whenever a highly acid stool showing faulty carbohydrate metabolism is found, for experience has already demonstrated the value of this procedure.

The fat content of the diet should also be carefully supervised. Certain patients, particularly those with thymic disturbances or spasmophilic tendencies, are apt to have faulty fat digestion and increased coagulability of the blood, and to show a tendency to form insoluble calcium salts in the intestinal tract.

Quite recently in America an absolute starvation cure lasting three to four weeks has been advocated. The results, however, though quite striking, are as yet too meager and cover too short a period of time to be of definite value.

Medicinal Treatment.—Medicinal aids in the treatment of epilepsy include drugs that are of benefit in the general hygiene of the patient, such as cathartics and tonics, those that are intended to combat certain specific

diseases whose amelioration is associated with improvement of the epileptic manifestations, as syphilis and malaria, and sedatives, whose purpose is to diminish the frequency and severity of the attacks or to arrest them.

Bromid has a direct effect upon the cortex, according to experimental evidence. It acts as an inhibitory agent, and under its influence electric excitability of the cortex is diminished. Its combining power has also been carefully worked out, and today we know that bromin ions replace chlorin ions in the body, which thereby loses in chlorin content during administration of the former.

The most constant indications of bromid overdosage are coated tongue, foul breath, lethargy and mental dulness, slurring of speech, slow pulse, staggering gait, and a heavy shower of acne. This combination of signs should serve as a warning that the limits of tolerance are passed, and the administration of the drug should be promptly suspended.

Combinations with other drugs have also proved of great value. Whenever it becomes necessary to support a weakened cardiovascular apparatus, a combination with digitalis is useful. Cases with vasomotor instability, evidenced by flushes, tachycardia, globus, etc., are most favorably affected by a combination with atropin.

Of the drugs other than bromids, only two deserve mention as possibly of more value. The first of these is epileptol, a condensation product of amido-formic acid. Its therapeutic effect consists in diminishing the frequency and severity of the grand attacks and bringing about cessation of the mild attacks. During the intervals the toxic effects of bromid therapy are absent.

In America, luminal enjoys a steadily increasing popularity and bids fair to displace bromid in the treatment of epilepsy. The mechanism by which its physiological action is obtained has not yet been worked out, and while it is safe to say that it probably has a direct inhibiting action on the motor cortex, the writer's experience leads him to believe that it also exercises a certain vasomotor control as well.

The best effects are obtained from a dosage of $\frac{3}{4}$ to $1\frac{1}{2}$ grains once or twice daily, given night and morning. Sometimes hypodermic administration may better serve the purpose, by which 1 grain of luminal sodium may be given two or three times a day.

The administration of pituitary extract either alone or in combination with sedatives will bring about a relief from attacks in certain definite anthropomorphic types, according to Tucker, Timme, and others.

Thyroid administration is also warmly recommended by the French and Dutch writers. More recently parathyroid in combination with luminal has come into use.

Surgery has proved rather disappointing except in very few instances. Operative interference should be undertaken whenever the signs of focal lesion, betrayed by prodromal Jacksonian attacks, are sufficiently clear-cut to warrant assumption of a definite circumscribed area as the point of surgical attack. In general, one may say that the best results are obtained whenever the seizures are of pure Jacksonian type and the lesion very small and circumscribed. Even though Horsley has reported favorable termination of attacks ten years after the onset, every patient should be operated upon as early as possible in order to prevent the possible development of genuine grand mal attacks. Little or no success has followed

incision of the epileptogenous zones in mixed types where the generalized convulsions develop after a period of Jacksonian phenomena and become firmly established.

The greatest success in the operative field lies in the removal of the causative factors in so-called reflex epileptic types. It is in this class that the many instantaneous operative cures are encountered, and it is fairly safe to say that whenever the diagnostic criteria of production of a fit by stimulation of the irritative focus are satisfied, removal of the focus will cure the epilepsy.

Mental Care.—The mental care of epileptics is of great importance. Not only do they need constant encouragement to maintain them at a proper level of effort to carry out instructions, but increasing watchfulness must also be employed to eliminate various sources of irritation and to show them how to adjust themselves properly to unpleasant situations—in other words, to establish the proper principles of mental hygiene.

Institutional treatment properly directed along strictly modern lines affords the best possible means of handling cases. Unfavorable home surroundings, illiterate, unsympathetic parents, the close unhygienic confines of urban life, the handicap which prevents participation in the games, pursuits, or occupations of social intimates, or a somewhat maudlin sympathy that fosters rather than corrects permanent character defects, form conditions that seriously interfere with an otherwise intelligent therapy, and furnish the best reasons for deciding upon an institutional course. In properly conducted institutions the epileptic may receive the benefits of a well-regulated hygiene, be taught to view his malady in its proper light, and learn to enjoy the inestimable advantages of an out-door life.

Edwin G. Zabriskie.

MIGRAINE

Definition.—Migraine is a periodic cephalalgia characterized by the absence of any local lesions which might occasion headache, and peculiar as regards the visual and oculoplegic symptoms and psychic phenomena which may accompany it. All migraine, except that of the abdominal type, may be considered headache, but all headache is not migraine. Migraine is characteristically periodic, and one definition of the condition is "a periodic headache caused entirely by eye-strain." This, however, does not really describe the severe, strange, unexplained constitutional disturbance to which the name migraine is properly applied. The term *ophthalmic migraine* is somewhat superfluous, because it is merely a separate name for the periodic headache associated with such visual disturbances as scintillating scotomata.

Etiology.—Migraine can be shown to be *hereditary* in every instance if heterozygous inheritance is carefully considered. Timme states that the hereditary factor in "migraine families" is the anatomical structure of the base of the skull and particularly that of the sella turcica. The existence of a constitutional *kinship between migraine and epilepsy* is shown in Buchanan's conclusion that migraine and epilepsy are transmitted from generation

to generation as the expression of the same underlying factor in the germ plasm; and his carefully amassed statistics seem to demonstrate that an individual with migraine is more likely to produce epileptic offspring than is an individual with epilepsy.

In the old conceptions, migraine was explained on the basis of injury, excessive work, or exhausting disease, but new ideas relegate such factors to secondary place. Excesses of work and the ill-effect of exhausting disease can be fully corrected without relieving the migrainous constitutional syndrome. Miller and Raulston point out that there is evidence to support the theory that migraine is definitely *anaphylactic* in nature and therefore in some measure comparable to hay-fever, asthma, and urticaria. Patients with migraine frequently have periods of relative immunity during which nerve strain, that would ordinarily bring on an attack, is without effect. These might be considered refractory periods corresponding to an anti-anaphylactic state, and they emphasize the points of similarity between asthma, which is certainly anaphylactic, and migraine. In each, the attacks are periodic, nervous influences are important in precipitating an attack, the disturbance frequently disappears temporarily after some prolonged infection, and pregnancy sometimes exerts a favorable influence. A certain kind of food has been known to institute an attack in both conditions. Migraine as well as asthma is often accompanied by eosinophilia. These points at most suggest by analogy that migraine is a sensitization disease. Brown believes that in migraine the condition of the gastro-intestinal tract and the character of the diet play at least a secondary or contributory rôle in producing the explosive phenomena. He divides cases of migraine into four groups: (1) Those associated with intake of more carbohydrate than can be utilized; (2) those associated with the intake of animal food, either in excess or of a type which sets up a specific reaction; (3) those few associated with true intestinal toxemia caused by the decomposition products of protein digestion which are possibly related to histamin; and (4) those associated with metabolic abnormalities which require complete avoidance of purin-containing foods. Timme believes that there are two classes of food which invariably precipitate attacks of migraine in predisposed individuals; *i. e.*, substances rich in iodin, such as fish, oysters, clams, and occasionally even spinach; and carbohydrates in excess.

Certain observers feel, on the other hand, that the etiology of migraine is preponderantly *endocrine* in character. Timme has noticed that hyperthyroid conditions, disturbances in the gonadal organs, thymic abnormalities accompanied by so-called suprarenal deficiency, and pituitary inadequacy (small and enclosed sella turcica) all lead to migraine. Since each involves a pituitary change, he believes that the fundamental cause is inherent in an hypophyseal-sellar disproportion. His discussion of such other etiological conditions as "fatigue states," "depressed states," "prolonged worry," and "food idiosyncrasies" is based on the conception that the process develops through pituitary disturbance either directly or from a secondary so-called hyperthyroid state. If migraine is a specific constitutional anomaly there must always be a single, common causative factor. Consequently there is merit in the effort of the endocrinologists to find this entirely necessary keystone of the arch in endocrinal situations such as the hypophyseal-sellar maladjustment.

Women are two or three times more liable to have migraine than men.

Morbid Anatomy.—The pathology of true migraine is not known at present, and probably cannot be discovered until the correlation of the sympathetic nervous system and the endocrine system is more fully known, and the phenomena of anaphylaxis are better understood.

Symptoms.—Just before an attack of migraine the patient may experience vague feelings of impending *malaise* for a variable number of hours. *Severe pains* of great intensity then develop, sometimes gradually, and sometimes with great suddenness. They are usually intense across the forehead, but may be focused back of or between the eyes; or be entirely occipital or temporal and limited to one side. In any individual the pain is usually in the same place in every attack. It is severe, incapacitating, and made worse by such environmental annoyances as jarring movements, bright lights, and loud sounds. During this period there are sometimes *flashes of light or dark and light spots* before the eyes or scintillating zigzag lights. The *visual acuity* may become dimmed or the *visual* fields contracted. Partial *oculomotor paralysis*, with temporary strabismus, sometimes arises and, in rarer instances, *peculiar odors or tastes*, *slight hemiplegia*, or *temporary aphasia*. Transitory states of *mild confusion* with apparent disturbances of perception may develop. It has not been shown that these are not based on the mental abstraction which the suffering occasions. *Vertigo* is frequent, and a distressing *tinnitus*, and usually nausea, which often leads to vomiting.

Disturbances of the sympathetic system are frequently evidenced by pallor, coldness and sweating of the hands and feet, unilateral hyperidrosis, high degrees of pupillary fixation (either dilatation or marked contraction), and excessive lacrimal secretion, or by alteration from normal in the salivary secretion. The *gastro-intestinal symptoms* are probably referable to the sympathetic system. In most cases they are associated with relatively mild cephalic pain, although the usual visual and vertiginous disturbances are present, with localization of the severe pain in the abdomen.

The attack is never febrile. It is not accompanied by leukocytosis; but in a large percentage of cases there is a *temporary eosinophilia* (5 to 16 per cent.). The pulse may be slow.

The attacks usually last one to three days, occasionally only a few hours. They recur at varying intervals, once or twice a month or even weekly, and in women are apt to coincide with the menses. At the menopause they are very likely to disappear.

In a few cases (about 7.5 per cent.) epilepsy and migraine are coexistent. The epilepsy may come in major attacks, but manifestations of *petit mal* are more usual in this association.

Treatment.—The initial treatment is the establishment of suitable *personal hygiene*. Sufficient and regular sleep, regularity of meals, avoidance of hurry and strain, and abstention from worry are essential. Toxic infections of the tonsils, teeth, sinuses, and intestines must be cured. Correction of pelvic abnormalities is essential, particularly if there are menstrual irregularities.

More *specific treatment* includes a multitude of unimportant measures, none of which have proved very successful. For the attack itself it is usually not possible to administer drugs. The proper conditions of solitude and quiet may be supplemented by such simple procedures as the application of cold and hot compresses, the use of menthol stick, and hot foot

baths. *Pyramidon, aspirin,* and similar products can be given, but stronger remedies, such as codein, are dangerous because they may produce an addiction to drugs. The administration of *calcium lactate* by mouth (30-grain doses) at the first sign of the approach of symptoms is claimed to abort an attack. The use of *benzyl benzoate* by Delorme in so-called ophthalmic migraine seems logical because this drug relieves spasm of the muscles of accommodation. *Phenolbarbital,* which may prove helpful in the attacks, may also be given in small doses during the intervals between attacks, and is said to diminish their number and severity. Sicard, Parof, and Forestier recommend intravenous injection of sodium carbonate in five to eight doses (1.5 to 2 gm.) at two- or three-day intervals.

Migraine of essential hypertension, chlorotic or anemic headache allied to migraine, and other allied states which are considered rheumatic or gouty need individual treatment.

In selected cases Sluder's *cocainization* of the nasal ganglion may be tried. In his hands this procedure has sometimes caused complete cure in migraine. The rationale of the method has not yet been shown.

The most interesting type of therapy is that based on the conception that the disease is anaphylactic. Boehnstadt began such work by treating migraine with placental extract. A newer procedure reported by Miller and Raulston consists of the intravenous injection of from 0.5 to 2 c.c. of a 5 per cent. solution of peptone. When peptone is given in small amounts there is little danger of anaphylactic shock, and these workers have never observed any untoward results or febrile reaction if the solution was sterile. The first injection is 0.5 c.c.; thereafter the dose is rapidly increased to 2 c.c. Usually the solution is injected twice a week until the headache disappears, and then weekly. With improvement, the intervals between injections are gradually lengthened to a month. If the medication is discontinued, the migraine sooner or later returns. The longest period of freedom, after discontinuance, was nine months.

Finally, there is endocrine therapy. Pituitary extract (whole gland substance, 0.1 to 1 gr. once or thrice daily, one hour after meals) may prevent attacks. Sometimes, however, the dose appears to stimulate the pituitary gland itself and must be reduced before it can be beneficial. Other glandular extracts have been given. The induction of an artificial menopause by the use of radium has cured some patients.

Thomas K. Davis.

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THE NEURALGIAS

"Neuralgia" is a term applied to various pains in the nerves, which follow the distribution of nerve-fibers, and do not cause structural change. Osler and McCrae believe that neuralgia is due to a functional disturbance of the central or peripheral extremities of the nerve, while Tyson and Fussell feel that it should be considered only pain of the nerve without organic change. It is rather difficult to distinguish sharply between neuralgia and neuritis, but if there is a distinction neuralgia is probably due to acute or chronic ganglionic affections, and neuritis to acute and chronic inflammation of the peripheral nerves.

TRIFACIAL NEURALGIA

(*Tic Douloureux*)

Trifacial neuralgia is a disease of the gasserian ganglion, which affects one or more branches of the trigeminal nerve, and is manifested by sharp, shooting, excruciating pains. The disease usually begins in middle life. The pain appears periodically, lasting for a few weeks, and in the beginning is followed by intervals of relief of from four to six months. It increases in severity and duration as the disease progresses, and the intervals of relief become shorter until the pain is almost continuous.

History.—Trifacial neuralgia was first described by Avicenna, an Arabian physician, as *tortura facies* (facial agony). Previous to 1900 various medical remedies (aconite, belladonna, and opium) were used in the treatment, with but little success. In 1891 Hartley and Krause devised their operation for ganglionectomy through the transtemporal route; and in 1898 Hutchinson advocated partial resection of the ganglion. Spiller in 1898 reported the division of the sensory root of the gasserian ganglion, and in 1901 the experimental work of Frazier and Spiller was presented to prove the efficacy and safety of such an operation over ganglionectomy. In 1902 Petres and Verger, and in 1903 Schlösser, described methods of injecting the peripheral branches of the fifth nerve with alcohol. At about the same time, Cushing developed a technic for dividing the sensory root, and also perfected the technic for avulsing the ganglion. Since then the palliative treatment has consisted of alcohol injection and peripheral avulsion, and the radical treatment of division of the sensory root. There have been minor changes in the operation, but most surgeons follow the principles laid down in the physiological extirpation or division of the sensory root, which gives permanent and instant relief from the neuralgic pains.

Etiology.—The cause of trifacial neuralgia is unknown. The suggestion that the condition is probably due to ascending neuritis following dental caries has been objected to by numerous physicians because there is no anesthesia or motor paralysis in the branches involved. Frazier believes that a sclerotic lesion of the ganglion may be the etiological factor, while Dana ascribes the probable cause to degenerative changes in the ganglion and nerve. It is fair to assume that the foregoing suggestions are fairly good, since the disease occurs in middle life or later; is prone to develop in patients suffering from arteriosclerosis, sclerosis of the brain or cord, and chronic diseases, such as migraine, nephritis, diabetes, and syphilis; and is likely to be associated with other types of neuralgia (intercostal or sciatic).

Trifacial neuralgia is not hereditary, although there are cases on record in which several members of the same family have been afflicted.

Symptoms.—In order of frequency the disease affects the infra-orbital division of the nerve, then the mandibular, and last the ophthalmic. The *pain* is described as shooting, stabbing, jabbing, flash-like, darting, zigzag, and lightning-like. As a rule, it is of short duration, and not continuous or

of a dull, aching type. Occasionally there is uneasiness, or a prickling sensation between the jabs of pain. The severe discomfort is brought on by eating or drinking hot or cold foods, talking, exposure to sudden drafts, and by washing the face or teeth. Patients say that certain areas along the course of the affected nerve are more sensitive than others; these are called "trigger zones," since touching them precipitates an attack of pain.

In 1922 the writer reviewed a series of 505 cases of trifacial neuralgia observed at the Mayo Clinic subsequent to 1910. Of these, 275 of the patients were males and 230, females. The average age on admission was fifty-four and one-half years, and the average duration of symptoms was eight and one-half years. Three hundred and twenty-seven of the patients had pain on the right side, 167 pain on the left side, and 11 on both sides. Three patients had pain in the ophthalmic division alone, 83 in the superior maxillary division alone, and 107 in the mandibular division alone. Forty-four patients had pain in the first and second divisions, 4 in the first and third divisions, 181 in the second and third divisions, and 77 in the first, second, and third divisions. In 6 instances a record had not been made of the branches involved. Besides trifacial neuralgia, 12 patients had chronic nephritis, 9 had syphilis, 51 had arteriosclerosis, 31 had sclerotic lesions of the brain or cord, 41 had migraine, 1 had intercostal neuralgia, and 7 had sciatica.

Complications.—Occasionally neuritis of the mandibular and the superior maxillary branches of the nerves may be confusing in a neurotic patient; such pains follow poor dental surgery with traumatization of nerve branches. Occasionally, also, an atypical trifacial pain of boring character, with exacerbations, occurs in the region of the superior maxilla under the malar bone; this cannot be relieved by injection of alcohol or by the radical operation and has been described by Sluder as sphenopalatine neuralgia, and by Frazier as a sympathetic pain relieved, occasionally, by superior cervical sympathectomy.

Diagnosis.—Trifacial neuralgia is accompanied by definite symptoms that are not readily confused with other pains of the face. The pain is characteristically periodic, severe, of short duration (a few seconds to a minute or two), occurs during waking hours, is brought on by external irritation, is almost always unilateral, and differs from the dull, aching, continuous type associated with *dental caries* or *sinus infection*. Furthermore, deep alcoholic injection of the trigeminal branches as they leave the skull affords complete relief, and produces anesthesia of the region supplied by those nerves. This does not occur with other types of pain of the face.

Prognosis and Treatment.—The disease at first is intermittent, but the pain gradually becomes more persistent until it is almost continuous, affecting first one branch, then a second, and often a third, and being present in one or all three branches simultaneously. It has never been known to disappear permanently without operative interference and, while drugs and other kinds of treatment have been thought to afford relief, the cessation of the pain during the administration of the particular form of treatment was probably merely a coincidence.

The two accepted measures for *palliative treatment* consist of peripheral avulsion, and deep injections of alcohol in the branches of the trigeminal nerve as they leave the skull. The average duration of relief following *peripheral avulsion* is eight months; avulsion cannot be repeated. The

deep alcohol injection, which is the best palliative therapeutic procedure, affords continuous relief for an average of nine months. The procedure is not altogether free from complications, but proves successful in about 75 per cent. of cases, and can be repeated a number of times. The technic described by Lévy and Baudouin, and modified by Patrick in 1907, is generally used.

The needle consists of a trocar and cannula, 8 cm. in length and 1.5 cm. in diameter, graduated in centimeters; the blunt end is constructed to permit the attachment of a 5 c.c. syringe. The area to be injected is prepared as for surgery. It may be anesthetized by local anesthetic, or the patient may be given gas or nitrous oxid until analgesia ensues. The needle may then be inserted without pain until it strikes the nerve. The patient indicates pain by resistance or movement. Complete anesthesia should be produced before the injection of 98 per cent. alcohol.

Radical treatment consists of division of the sensory root of the gasserian ganglion and gives instant and permanent relief. It should be advised after two or three injections of alcohol, which serve to teach the patient that numbness must be accepted in lieu of the excruciating pain. The operation is now performed through the transtemporal approach extradurally, with ligation of the middle meningeal or plugging of the foramen spinosum, exposure of the third branch, the gasserian ganglion and the sensory and motor roots, division of the sensory root, and preservation of the motor root. It produces anesthesia over the side of the face and forehead in areas corresponding to the divisions of the trigeminal nerve. On account of the resulting anesthesia of the cornea, it is necessary to protect the eye from dust and wind with automobile goggles or specially prepared glasses. The operation is attended with no greater surgical risk than appendectomy in a patient of the same age, and, since it relieves the pain and permits the individual to continue his regular vocation, should be advocated strongly in preference to long years of suffering and invalidism.

GLOSSOPHARYNGEAL NEURALGIA

Glossopharyngeal neuralgia affects the petrosal and the jugular ganglion of the glossopharyngeal nerve. It is similar to trifacial neuralgia in that the associated pains are spasmodic, excruciating, and lancinating, but differs in that the pain radiates from the pharynx and tonsillar fossa to the ear. The pain may be brought on by swallowing or yawning, lasts from a few seconds to a minute or two, and recurs many times during the hour. As in trifacial neuralgia, the attacks are intermittent, but are of shorter duration and separated by longer intervals of relief.

History.—In 1910 Weisenburg described the glossopharyngeal-nerve syndromes, and in 1920 Sicard and Robineau described 3 cases of "algie velo-pharyngée essentielle," the first two of which were seen in the French Army in 1916 and 1917. In both the pain had persisted for several years and was not continuous, but recurred frequently day and night in extremely acute paroxysms on the least movement of mastication, deglutition, or speech. The patients developed suicidal tendencies on account of the apparent incurability of the condition. They were treated by section of the glossopharyngeal nerve and the pharyngeal branches of the vagus, and by ablation of the superior cervical sympathetic ganglion.

Etiology.—The specific cause of glossopharyngeal neuralgia is unknown, but in all probability it is an affection of the petrosal and jugular ganglion of the glossopharyngeal nerve, because the pain is relieved by peripheral avulsion of the glossopharyngeal nerve at its exit from the jugular foramen

The fact that the sensory distribution comes through the pharyngeal, tonsillar, lingual, and tympanic branches of the ninth nerve accounts, no doubt, for the location of the pain in the pharynx within an apparent trigger zone, and in the tonsillar area, and its production by swallowing, yawning, and so forth, with radiation to the tympanum.

Symptoms and Diagnosis.—Glossopharyngeal neuralgia simulates trifacial neuralgia in its occurrence, duration, repetition, and character, but differs from it in its distribution, and the location of a trigger zone in the tonsillar fossa. It is more often brought on by swallowing than by chewing, cannot be evoked by rubbing the face, and only occasionally by rubbing the ear. It also differs from trifacial neuralgia in that the pain radiates from the pharynx and tonsillar area through the neck to the ear, particularly to the tympanum. It is possible to evoke paroxysms of pain by stimulating the pharynx, but difficult to produce them if the pharynx and tonsillar area have been thoroughly cocainized; such anesthesia does not inhibit paroxysms of pain in the maxillary and mandibular branches of the trigeminal nerve in *trifacial neuralgia*. Glossopharyngeal neuralgia also is unlike trifacial neuralgia, since it is impossible to inject the nerve with alcohol on account of its close proximity to the vagus, hypoglossal, and spinal accessory nerves. Temporary relief can be obtained, however, by peripheral avulsion just as in trifacial neuralgia.

Doyle emphasizes the diagnostic symptoms, and also the sensory and gustatory changes in glossopharyngeal neuralgia, and states that in 2 patients who had had extracranial avulsion of the glossopharyngeal nerve there was a sense of fulness on the side of the pharynx operated on, complete anesthesia to pain, temperature, and tactile sensation over the entire half of the inferior aspect of the soft palate, and anesthesia back to 1.5 cm. from the posterior border of the upper aspect of the soft palate. That portion of the pharynx between the level of the hard palate and the pyriform fossa was likewise anesthetic to pain, tactile, and temperature stimulation. Sensations remained normal over the posterior half of the nasopharynx and over all of the nasopharynx above a line drawn through the hard palate, as well as over the epiglottis and the upper aspect of the larynx. The sensations of taste (salt, sweet, bitter, and sour) were absent over the entire half of the tongue on the side operated on.

Prognosis and Treatment.—While the pain is primarily intermittent, it continues to recur until it is almost continuous. It does not cease spontaneously. On account of the depth of the glossopharyngeal nerve and its intimate association with the hypoglossal nerve and vagus it is unwise to attempt an *injection of alcohol*. *Intracranial division* proximal to the ganglia is necessary for permanent relief. Since at the onset the pain rarely lasts more than one month, *anodynes* and occasionally *hypnotics* may afford relief. *Peripheral avulsion* affords relief for a period of from a few months to one to three years in length, according to the success in avulsing the fibers from the petrosal ganglion. Inasmuch as this operation requires extensive dissection, intracranial division above the petrosal ganglions through a cerebellar approach is advisable.

SCIATIC NEURALGIA

The term "sciatica" is applied to painful conditions of the sciatic nerve or its distribution. The condition is usually considered neuritic, but since

in all probability there is an essential sciatica or ganglionitis of the lumbosacral ganglion, the condition may be classified as sciatic neuralgia. Pains along the sciatic nerve due to various forms of arthritis of the lumbar spine and of the lumbosacral and sacro-iliac or hip-joint; pains due to anatomical anomalies, such as long transverse processes of the fifth lumbar vertebra; pains due to straining the sacro-iliac joint, and those due to pelvic tumors are discussed under the head of Sciatic Neuritis.

Etiology.—Sciatic neuralgia is more common in males than in females, and develops usually in the fourth and fifth decades of life, although it may occur in the third, sixth, and seventh decades. The incidence of trifacial and glossopharyngeal neuralgia is similar. The condition is invariably associated with the history of a chronic infectious focus, or an acute infection, and may be brought on by exposure. True sciatic neuralgia is probably caused by infection of the ganglion (ganglionitis) or by an inflammation around the ganglion (periganglionitis), since the evidence of neuritis which usually produces sensory and motor disturbances (paresthesia, anesthesia, paralysis, and atrophy) is absent. The course of the nerve may be tender to pressure and extension of the leg may cause pain; these manifestations are analogous to the pain which is produced in trifacial neuralgia on touching the area affected, or on movement of the facial muscles. Sicard and Cathelin have attributed sciatic pain to inflammatory lesions of the nerve roots within the canal, outside the dura, which are embedded in a mass of adipose, cellular tissue continuous with the fatty layer surrounding the dura, and have termed the condition "funiculitis." This conception is probably incorrect, however, because true sciatic neuralgia is relieved at least temporarily by injection of novocain and physiological salt solution into the epidural space of the sacral canal, and this would be impossible if the lesion were sciatic neuritis or funiculitis. Probably therefore inflammation of one or more of the ganglia of the sensory roots is the cause of the pain.

Symptoms.—The most constant and troublesome symptom is the *gnawing and burning pain* over the distribution of the sciatic nerve. This may at first be mild, but it soon becomes so intense that it incapacitates the patient, prevents his walking with ease, and makes flexion of the leg on the thigh difficult when the leg is extended. At the onset the pain is usually localized in some area supplied by the nerve rather than spread along its course. In some instances it is in the lumbosacral region only, in others in the hip-joint, the posterior area of the thigh, the postpopliteal space, the calf muscles, or on the outer surface of the foot. Sciatica may persist for a few weeks or several months, may recur, and be so severe as to confine the patient to bed. When lying down patients prefer to lie on the unaffected side, with the thigh and leg slightly flexed. If the disease is protracted, the *Lesague sign* is usually present and the *tendon of Achilles reflex* is lost. *Fibrillary contractions* may also occur, but the reaction of degeneration is seldom obtained. In rare instances *herpes zoster* not unlike that affecting the intercostal nerves may develop over areas supplied by the sciatic nerve. In addition to the pain there is generally *evidence of chronic infection* of either the tonsils or apices of decayed teeth; or there may be sinus disease. Occasionally acute general infection, intercostal neuralgia, or trifacial neuralgia accompanies these manifestations.

Diagnosis.—The diagnosis cannot always be made readily. The pos-

sibility of *arthritis, disease of the sacro-iliac* or *hip-joint, surgical anomalies,* and *pelvic tumors* should be ruled out before treatment is attempted. Occasionally, as a diagnostic measure, from 20 to 60 c.c. of 0.5 per cent. novocain in physiological salt solution is injected into the epidural space through the sacral canal. This always produces pain in true sciatic neuralgia and rarely, if ever, in other diseases producing sciatic pain.

Treatment.—The most essential factor in the treatment of sciatic neuralgia is the determination of the cause and its elimination. It is highly important to remove all foci or questionable *foci of infection.* This usually aggravates the pain during the first week or two, but in most cases eventually gives relief. If the pain is severe, it is advisable to relieve the patient temporarily by *injection of novocain* (0.5 to 1 per cent.) and *physiological salt solution* into the sacral and lumbar canal. This always produces pain on the affected side and not on the normal side, and the discomfort is always felt at the point of tenderness and in the originally painful area, instead of along the course of the nerve. Neither pain nor relief is experienced by patients who do not have true sciatica, but suffer pain referred along the sciatic nerve or produced by arthritis or anatomical anomalies. In true sciatic neuralgia the pain disappears immediately after injection, with only rare consequent anesthesia or motor disturbance, and the patient can walk from the operating room. The old treatment of *stretching the nerve* and injecting it is of little or no value, but may occasionally slightly relieve pain due to one of the arthritides. In addition to these measures *rest in bed* and the administration of *acetyl-salicylic acid* (10 gr. three times a day) and of *Carlsbad salts* for purgation are desirable. The injection may be repeated two or three times if necessary.

CERVICO-OCCIPITAL NEURALGIA

Cervico-occipital neuralgia is a painful affection of the four upper cervical nerves, chiefly of the great occipital branch of the posterior division of the second cervical nerve.

Etiology.—Although the cause is similar to that of sciatic and intercostal neuralgia, that is, a *focus of infection* or an *acute infection,* and occasionally *exposure,* the disease is probably due to *specific infection of the dorsal ganglia* of the four upper cervical nerves.

Symptoms.—The symptoms are excruciating, more or less jabbing *pain,* which radiates over the area supplied by the occipital nerve, and *muscular spasms* and *stiffness of the neck.* The skin over this area is highly sensitive to touch. The point of greatest tenderness is at the exit of the occipital nerve, which is approximately half-way between the mastoid process and the first cervical vertebra. Next in order are the areas over the parietal eminence and between the sternomastoid and trapezius muscles.

Diagnosis.—The diagnosis is often confused with the neuritis due to *cervical arthritis.* The differentiating diagnostic features in cervico-occipital neuralgia are the primary affection of the occipital nerve and the intensity of the pain. The characteristic posture of patients suffering from this disease is slight flexion of the neck with the head held rigid, and the hand placed apprehensively at the back of the head to prevent the sensitive area from being touched. Cervico-occipital neuralgia is generally unilateral, but it may be bilateral; cervical neuritis with arthritis is usually bilateral.

Prognosis and Treatment.—The disease persists for several months and

may then disappear if the infection has been removed. It may recur much as does sciatic neuralgia.

The *treatment* consists of removal of all *foci of infection*, and local application of *counterirritants*. *Injection* of alcohol into the cervical roots, as they leave the skull, is frequently resorted to, but is rarely successful. *Anodynes* and *hypnotics* are necessary to alleviate the pain; if these fail, *intraspinal division of the sensory roots* becomes necessary.

INTERCOSTAL NEURALGIA

Intercostal neuralgia is a painful affection of the intercostal nerves which may be associated with or followed by herpes zoster. It may also occur without an eruption of the skin and exist for months before subsiding. It is probably caused by an infection of the dorsal ganglia, but occasionally hysterical patients complain of intercostal pain without disturbance of the ganglion. The disease runs a course similar to that of cervico-occipital neuralgia, and the treatment is also similar.

ATYPICAL NEURALGIA

Atypical neuralgia includes the various types usually classified in textbooks of medicine as *definite neuralgias*. The term "atypical neuralgia" is used because in many instances the pain is due to neuritis or is referred along certain nerves as the result of various organic diseases and anatomical anomalies.

BRACHIAL NEURALGIA

"Brachial neuralgia" is a term applied to the condition in which there is pain over the area supplied by the four lower cervical and the first thoracic nerves, tenderness in the axilla, over the deltoid, behind the elbow, and in front of the wrist. The pain is dull and aching, and may persist for a few weeks to a few months, or longer.

LUMBO-ABDOMINAL NEURALGIA

Lumbo-abdominal neuralgia affects the posterior fibers of the lumbar plexus, particularly in the ileoscrotal region. The pain is usually unilateral in the region of the iliac crest or along the inguinal canal, in the spermatic cord, in the scrotum, or around the anus. It is sometimes associated with a sacral neuralgia, and causes the patient to complain of pain around the anus and the perineum.

COCCYGODYNIA

Coccygodynia is regarded as neuralgia of the coccygeal plexus. It is generally considered a functional disorder, although it is occasionally attributed to injury of the coccyx. It is more common in women than in men, and is aggravated by a sitting posture. The disease is extremely difficult to cure.

PHRENIC NEURALGIA

Phrenic neuralgia usually occurs in the lower part of the thorax, but may be referred to the supraclavicular region of the neck. The pain is aggravated by breathing movements, coughing and deglutition, and is usually associated with diaphragmatic pleurisy or pericarditis. In all probability it is due to a form of neuritis.

VISCERAL NEURALGIA

Visceral neuralgia is more common in women than in men, and is often associated with neurasthenia and hysteria. The pain is usually in the pelvic region, particularly around the ovaries, but the gastro-intestinal tract and kidneys may be affected. The cause of the pain is questionable, since it is difficult to demonstrate a lesion in the organs affected or in the nerves supplying them.

NEURALGIAS OF THE NERVES OF THE FEET

Cases of neuralgia of the nerves of the feet are divided into three groups: *Group 1, painful heel:* Painful heel is equally common in men and women, and is so severe as to interfere with walking. It is thought to be due to bony spurs or to gonococcal infection; evidence of arthritis is not always present. *Group 2, plantar neuralgia:* The pain in plantar neuralgia is associated with numbness, tingling, and hyperesthesia in the tips of the toe and in the ball of the great toe. Occasionally there is sweating on the plantar surface of the foot. In many instances the patients have some associated disease, such as typhoid fever. *Group 3, metatarsalgia:* Metatarsalgia is described by Morton as a painful affection of the fourth metatarsophalangeal articulation; he ascribes it to pinching of the metatarsal nerve. Relief is usually afforded by operative intervention.

ERYTHROMELALGIA

Erythromelalgia was first described by Weir Mitchell as a vascular change of vasomotor origin which causes hyperemia or cyanosis of the skin of the feet and ankles. It is associated with severe burning pain in the heel or in the sole of the foot. Relief is obtained by elevating the feet or by placing them in cold water. The disease is probably due to neuritis of the vasomotor nerves of the vessels.

SLUDER'S NEURALGIA

Sluder's neuralgia is a painful affection of the sphenopalatine ganglion, which causes what Sluder calls "a lower half headache" with boring and burning pain in the area of the superior maxillary and a radiation of the pain into the neck and the shoulder. It is frequently associated with ophthalmic migraine. Sluder has been able to relieve certain of these conditions by the injection of alcohol and phenol into the sphenopalatine ganglion.

OTALGIA AND MASTOIDALGIA

Lillie describes otalgia and mastoidalgia as pain in the region of the ear and of the mastoid, without any obvious evidence of inflammation. Wilson believes that they are brought about by a referred pain along the auriculotemporal nerve.

SYMPATHETICALGIA

The pain in sympatheticalgia is severe, boring, and burning, and is in the superior maxillary region. A few patients have been relieved by removal of the superior cervical sympathetic ganglion; others have been partially or completely relieved by removal of the superior cervical sympathetic ganglion alone, and by the removal of the superior, middle, and inferior cervical ganglia with their corresponding nerve trunks. It has been

generally assumed that pain fibers are not carried by the sympathetic nervous system, but owing to the striking results following sympathectomy further study will be required to clarify this subject.

CAUSALGIA

(*Thermalgia*)

"Causalgia" is a term applied to burning pains in nerves following gunshot wounds, and is associated with marked hyperesthesia, glossy skin, and hyperemia. It occurs most frequently in the median and in the sciatic nerves. The cause of the disease is not known, but it is generally ascribed to irritation of the peri-arterial sympathetic fibers. Since the median and the post-tibial nerves have a large number of vasomotor fibers it is inferred that this is a probable explanation for these nerves being affected more often than others. The condition has been observed quite frequently in veterans of the World War.

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PROFESSIONAL CRAMP

A professional cramp is a special form of occupational neurosis. Cerebral in origin, it is best described as a focal fatigue ataxia. In mechanism it is allied to tic and especially to stuttering. The commonest variety is the so-called writer's cramp, though we also meet with similar conditions in the cramp of typists, cutters, telegraphers, cigarmakers, and so on. Every type of musician has been the subject of the condition. It shows itself in an inability to use a part, usually a hand or arm, to do a particular movement. The extremity is normal for all motor actions except the particular one. When a person is learning an occupation, he risks no cramp of the kind under discussion. When he is expert and is having to repeat a movement over and over for long hours at a time, he may develop it. The patient with writer's cramp may no longer be able to write with a pen, though able to use his hands and fingers skilfully in playing a piano. This is because there is a cerebral fatigue, not a muscular fatigue, to blame. At first the patient may have only a weakness or slight cramping which makes the full completion of the movement difficult. Later the difficulty may be an effective paralysis of the hand when the particular movement is attempted. In some instances tremor may be added to the situation when the patient is endeavoring particularly to overcome it.

True professional cramp is free from the sensory or vasomotor signs of neuritic disease and leaves the muscles normal in contour and substance. Occasionally slight grades of neuritis may develop as a co-existing difficulty.

The chronic character of a majority of cases of professional cramps needs emphasis. In treatment a temporary or permanent change in occupation is required with well-apportioned diversion. At this point motor activity of the affected parts for all movements in general should be insisted upon. Physiotherapy and general tonic hygienic treatment are indicated, the former best directed not alone to the parts disabled. Mental conflicts, important etiological factors in some instances, must be solved by mental analysis, Freudian or otherwise. In writer's cramp the introduction of different motor maneuvers, such as writing with more shoulder movement and less wrist, is helpful, and often it is wise to have the patient train himself

to use the other hand. These shifts in the form of the motor endeavor need to be encouraged. In all, cure is sought along lines of re-education combined with physiotherapy and skilfully controlled rest. Drugs are not indicated except as placebos. Some cases, fortunately, come to a spontaneous quiescence.

THOMAS K. DAVIS.

THE NEUROSES

HYSTERIA

Definition.—No very accurate definition can be given for a disorder so protean in its symptoms in all physical and mental fields.

We may say, however, that hysteria is a psychoneurosis founded on a basis of low vitality, characterized by general psychic weakness with an undue susceptibility to suggestion and autosuggestion which at last lead to perversions of behavior and loss or perversion of motor and sensory function.

Originally named for the uterus, disorders of which were supposed to cause the disease, it was long ago found to have no such association and to be very common among males as well as females.

Just as fear is a fundamental normal attribute of human nature, which in neurasthenia and psychasthenia becomes the dominant psychic symptom, so suggestibility, also a normal fundamental and necessary part of human make-up, becomes in hysteria the outstanding factor.

Etiology.—It is by no means certain that hysteria may not have as an important physical basis some disorder of metabolism of the nervous system similar to that which seems to underlie other psychoneuroses, such as neurasthenia and psychasthenia.

It is a very common disease in both sexes in early life, especially during puberty and adolescence. No doubt hereditary neuropathic disposition plays a certain part, and some races, such as the Slavic, the Latin, and the Jewish, are more prone to its development than others.

Mental and physical stresses and strains are exciting causes, emotional shocks, traumata, enfeebling physical diseases, intoxications by drugs and alcohol, and overwork.

Unconscious imitation with all the curious manifestations of mob and crowd psychology may develop hysteria in groups of people, as in religious gatherings, in schools, convents, prisons, armies, and crusades. It is well to keep this type of rather normal group-suggestibility in mind for the purpose of understanding better the abnormally heightened suggestibility of the hysteric. We see a similar psychological condition in the stampedes of the lower animals. Hysterical epidemics have often been portrayed in history—the Crusades for two hundred years costing seven million men, the children's crusades all over Europe, the flagellants of the thirteenth century who spread everywhere from Italy, the dancing mania, the torturing and burning of witches in the fifteenth century, and onward under the idea of demoniacal possession which carried off hundreds of thousands of men,

women, and children all over Europe and even in America, antisemitic manias, the historical speculative manias, and great religious revivals. These are group exaggerations of normal suggestibility. And it is to be borne in mind that suggestion and unconscious imitation are the foundation of all education, of customs, manners, morals, dress, in fact, of the whole behavior of any race of mankind. Non-conformity is taboo, and success in life depends upon being one in the chain of the Bandarlog. If you let go of the tail in front and free your own tail you are a non-conformist and suffer the consequences. But probably most of the progress of humanity, such as it is, has been made by the non-conformists, those who have held back from the hysterical runs of the Bandarlog into crusades, manias, and great wars for some flattering illusion and taken time to think.

The individual who through mental strain or shock or through some physical enfeeblement loses all higher controls, uncovers this old fundamental substratum of suggestibility, and becomes as a straw blown by the wind, subject to every suggestion from without and the autosuggestion of his own dreams and fancies.

Symptomatology.—As has been hinted before, the symptoms of hysteria are protean. Almost every disease may be simulated. Yet there are certain distinguishing marks in the hysteric, not present in all, but in most cases, that may be considered the stigmata of this disease, such as emotional lability shown in alternating laughing and crying, the ball in the throat or globus hystericus, varying anesthesias and analgesias of the tactile sense and inhibitions of the special senses, contraction of the visual field, dyschromatopsia, hyperesthesias, tremor, choreiform movements, muscular weaknesses, and in the mental field weakness of will, absent-mindedness, amnesias, abnormal suggestibility, and a morbid craving for sympathy which sometimes leads to voluntary simulation and fraud. Another characteristic stigma is that of equivalence, the not unusual transfer of one symptom to another, such as a hemianesthesia or hemiparesis showing itself on one side of the body at one time and later on the opposite side. The general symptoms of hysteria are usually divided into two large classes—the major and the minor. We are not so much concerned with major hysteria in this country because it is comparatively rare.

Major Forms include varieties of somnambulism, ambulatory automatisms, prolonged sleeps which may last for weeks or months, double personalities, and hystero-epilepsy. Hystero-epilepsy in its more serious manifestations with opisthotonos, cataleptic poses, and marked convulsions, unusual in America, is, in its more moderate types, not so uncommon. After some emotional upset a patient has laughing and crying spells, a globus hystericus, possibly pains arising in various parts of the trunk, and then falls into a general clonic convulsion strongly resembling epilepsy. There is apparent loss of consciousness. The movements are rather irregular and disorderly and not as rhythmic as in true epilepsy, and are often accompanied with noisy moans, groans, and ejaculations. After a time the turmoil subsides and the patient gradually regains consciousness with considerable emotional expression. Sometimes a cataleptic condition supervenes lasting for hours. The patient never falls in such a way as to hurt herself, has no ecchymoses of face, neck, or conjunctivæ, no biting of tongue, and no involuntary defecation or micturition, as happens in true epilepsy. Neither is there a true epileptic cry or the early tonic

rigidity with cyanosis. After the hystero-epileptic attack there is usually evidence of much gas in the intestines and a large amount of clear urine is passed.

Minor or Common Forms.—There is no variety of organic paralysis that hysteria may not simulate—monoplegia, hemiplegia, paraplegia, even occasionally diplegia. The most common type is hemiplegia, next paraplegia, and third monoplegia. The general explanation of all hysterical symptoms as due to some fixation of idea, while not easily applicable to them all when we ponder the subject deeply, seems nearer true as the chief factor in these paralyses. The patient thinks he cannot move his arm or leg on one side of his body, therefore he cannot. Babinski said, "A phenomenon is hysterical when it can be produced by suggestion and cured by persuasion." There is no doubt in these paralyses that as soon as the patient is persuaded that he can move the parts, they move. The paralysis may come on suddenly or gradually and last for days or years. It is rare to find complete paralysis of all the muscles as in organic cases. Anesthesias or hyperesthesias are frequent concomitants. The deep reflexes and the electric reactions are normal. The muscles may be flaccid or rigid, giving rise to *hysterical contractures*. Sometimes the contractures subside during sleep and always under general anesthesia.

The gait in hysteric hemiplegia is characteristic, the dragging of the paralyzed limb straight behind instead of the semicircular swing outward of organic hemiplegia. The Babinski reflex is never present in hysterical cases, nor does one find ankle clonus. The cutaneous reflexes are normal in hysteria. There are no atrophies. Anesthesias when observed are deeper in hysteria than in organic paralyses, and have distributions peculiar to hysteria, corresponding to the patient's idea of what lost sensation should be rather than to any anatomical basis as in organic types. There is something mental in the anesthesias of hysterics. They do not know that it exists until it is pointed out to them, whereas every organic anesthesia is discovered by the patient very quickly (as in local nerve lesions, tabes, syringomyelia, and the like).

Sometimes the ocular muscles are affected, and we have diplopia, strabismus, spasmodic oscillations of the eyes, etc.

Astasia-abasia is a type in which the patient is unable to stand or walk (that is the meaning of the words), though when lying down they can move every muscle and limb perfectly, and there are no signs of organic disease.

Aside from the sensory motor disorders just described, we may have hysterical aphonia, blindness, deafness, anorexia, singultus, dyspnea, vomiting, phantom abdominal tumors sometimes simulating pregnancy, pains and neuralgias in any part of the extremities or viscera, the so-called hysterical joints (severe pains most often in the hip- or knee-joints), anuria and polyuria, edema, local skin lesions or bleeding (stigmata), tremors, tics, and choreiform spasms, general emaciation, trance states, and fever. In fact, the symptoms of hysteria are legion and may, as before stated, simulate almost every organic disease.

Deception and Fraud.—There is no doubt that a common feature in hysteria is a morbid craving for attention or sympathy. This leads sometimes to the assumption or exaggeration of symptoms. Actual fraud may not be frequent, but it is sufficiently so to warn the physician to be on his guard. The writer has known patients to put milk in the urine, to put

small pebbles resembling calculi in the urine, to produce cutaneous lesions, to heat or squeeze a thermometer to make it register high temperature, to write mischievous anonymous letters, to trick relatives into the idea that the home is haunted, and to perform all sorts of bizarre actions in order to occupy the center of the stage in their particular drama.

Course and Prognosis.—The course of hysteria is apt to be chronic, though many of its episodes are often miraculously relieved by suggestion of physician or priest. There is a tendency to recurrence of its accidents under physical or mental stress. Very often under proper management the disorder may be permanently alleviated or cured. Young people recover more easily and fully than older subjects. The major types, especially in older people, have a very poor outlook.

Diagnosis.—After seeing a few cases, one becomes familiar with the hysterical character. Its very polymorphism is a helpful aid, except perhaps where it mimics some obscure abdominal disease. From what has already been said there should be no difficulty in differentiating hystero-epilepsy from true epilepsy, or hysterical paralysis from organic paralysis. Outside of these prominent manifestations we are guided in diagnosis by the essential stigmata of hysteria—in the mental field by the suggestibility, marked absent-mindedness, reductions in consciousness, alternations in the distribution of symptoms—in the physical field by variable isolated and geometric areas of anesthesia and retraction of visual and color fields.

One should search for the suggested idea which is the basis of the peculiar symptom, anesthesia, paralysis, contracture, spasm tic, blindness, deafness, aphonia, etc. The Freudian hypothesis is altogether too sweeping, and the cases are very rare in which a suppressed sexual complex is the foundation. In most cases the causal idea is easily discovered without psychanalysis. Traumatic hysteria has its obvious etiology, and the relation between idea and symptoms is clear, as in accidents of all kinds and war. Literature is full of other readily ascertained associations between suggestion and stigma. A woman shocked at seeing a fallen rider dragged by the foot developed paralysis of her foot. A man developed hysterical vomiting after nursing a patient with gastric cancer. A patient of the writer's developed blindness because of the repulsive ugliness of her husband. Sometimes a preceding weakness in some organ or function determines the localization of the disorder, as, for instance, where a girl, a stammerer, after a violent emotional stress becomes dumb, or a patient having had an old rachitic leg develops hysterical paralysis of this weaker member after an emotional shock.

Treatment.—The cardinal points in the treatment of hysteria may be summed up as isolation from home and relatives, improving the metabolism of the nervous system, and psychotherapeutic re-education.

Change is for anyone in itself a tonic, and the removal of an hysteric patient from the environment in which the malady has developed and from the too solicitous care and sympathy of relatives is paramount. The great success of Weir Mitchell's method in these cases lay in this isolation, his very careful overfeeding and fattening process, and psychotherapeutic talks and suggestions by a personality with great psychotherapeutic understanding and remarkable common sense. He laid such stress upon the nutritional foundations of cure in all the psychoneuroses that his book de-

scribing his method was called "Fat and Blood." We should not nowadays attach too much importance to the rest cure; rather as a part of the system of re-education we should employ every suitable type of occupational therapy. It is necessary to seek to discover in such patients any old or latent interest in any form of occupation, arts and crafts, languages, science, music, painting, athletic games; in fact, run the gamut of possible interest, and, having found it, develop it to the fullest extent. This is distraction, the suppression or forgetting of all the incidents of illness in a new life full of the ambitions and eager activities of the normal world.

The sagacious physician will not be too strongly misled in the handling of these cases by such unverified hypotheses as Freudian psychanalysis, endocrinology, and focal infection. What if any part these factors play in the etiology of the psychoneuroses is yet to be demonstrated; at present their all too prevalent exploitation has led chiefly to harm.

Aside from the great general indications for treatment just referred to, there are special adjuncts, often helpful, such as electricity, tonics by mouth or hypodermic injection, hydrotherapy, massage and physical culture, and the like. At one time hypnotism was considerably used, but found to be dangerous, and is now quite abandoned.

Frederick Peterson.

TRAUMATIC NEUROSIS

"Traumatic neurosis" is a term applied to the functional nervous syndrome which follows accidents unaccompanied by any actual organic lesion.

Only in the last thirty years have we understood clearly the various organic lesions that are caused by accident, and separated them from the innumerable neurotic manifestations of neurasthenic, hysterical, or hysteroneurasthenic nature that so commonly follow accident. Organic changes are often combined with neurotic, hysterical, and neurasthenic syndromes; and simple neurasthenia and hysteria may occur alone. The litigation consequent to so many accidents often emphasizes the symptoms, causes malingering which may complicate diagnosis, and by suggestion upsets hysterical individuals when they are subjected to frequent medical and legal examination. More ample knowledge of the anatomy and physiology of the brain and spinal cord, of the syndromes of hysteria and neurasthenia, and of the effect of fright and shock on the nervous system greatly aids diagnosis. The trauma which evokes neurosis is not necessarily physical, but may be psychic (fright or severe mental strain). If there are no organic lesions the condition falls into one of three categories: traumatic neurasthenia or psychasthenia; traumatic hysteria; traumatic hysteroneurasthenia or hysteropsychasthenia.

Traumatic Neurasthenia or Psychasthenia.—When trauma is the cause the syndrome may be marked by certain symptoms, such as irritability, pain in the back, depression, insomnia, general weakness, and vasomotor disorders. The neurosis usually develops a few weeks after the accident.

Traumatic Hysteria.—In traumatic hysteria the stigmata of hysteria are marked, and do not differ from the group of symptoms described in another chapter—anesthesia, hyperesthesia, concentric limitation of the visual field, paralysis, contractures, tremor, inco-ordination, ties, amnesia, suggestibility, lability of the emotions, etc.

Traumatic Hysteroneurasthenia and Hysteropsychasthenia.—In traumatic hysteroneurasthenia and hysteropsychasthenia many of the symptoms of both hysteria and neurasthenia or psychasthenia are present, although one syndrome may be more prominent than the other. The outlook for recovery is usually good, but the course of the disturbance is as long as that of ordinary neurasthenia and psychasthenia, and may be much longer if the patient is anxious and troubled by indefinite litigation. The sooner a suit is settled, the better the prospects for an early cure. Some individuals do not recover, a few grow worse, and some very rare patients suffer an insidious organic disorder of the nervous system which is difficult to recognize in the early stages. The therapeutic measures described for other almost similar disorders are applicable in these cases.

FREDERICK PETERSON.

SHELL SHOCK

(*A War Neurosis*)

The war neuroses naturally include a large number of conditions (neurasthenia, psychasthenia, hysteria, etc.) which develop among soldiers not only during actual warfare, but in camps far from the field of battle, and among the women left at home or doing war work. They are due to the mental and physical stresses incident to the conditions of war. These neuroses do not differ in any essentials from the ordinary type of the same disease prevalent at all times. It is difficult to find a better name than *shell shock* for the particular war neurosis which generally originates in the mental or physical traumata of battle.

Etiology.—As long ago as 1545 Paré mentions the "Wind of the Ball" as doing damage to soldiers who were not in any way physically touched by a cannon ball; and in several places in the Medical and Surgical History of the War of the Rebellion reference is made to the alleged traumatic effects of the "Wind of Balls." The term "shell shock" was, of course, unknown at the time, and this history contains large numbers of cases which were probably shell shock and not understood, but which were considered sunstroke, nostalgia, malaria, and various organic disorders. One army surgeon of that day, however, Dr. George Burr, has the honor of having first recognized and described this type of war neurosis in the United States. But the shells of those days were insignificant as compared with those of the recent Great War. In modern warfare the "Wind of the Ball" has become a real fact and not merely a form of speech, for it is recorded that the expansion of the gases alone in these terrific explosions has caused death. Mott found petechial hemorrhages in the brain in such cases. With these modern high explosive shells we have to deal not only with the physics of gas expansion, but with the poisons of the gases themselves, with the force which could throw the victims some distance or bury them under earth and débris torn up by contact with the ground or trenches, and with the terrifying mental effects of the violent detonations. It is not always easy under such circumstances to determine whether or not some patients with apparently only the usual functional symptoms of a neurosis have some actual, minute, and undiscoverable lesions in the central nervous system. No doubt, as in the neuroses previously described, a weak nervous constitution predis-

poses to shell shock, but to the new horrors of modern warfare the strongest constitution will at times succumb.

Symptoms.—The symptoms are those familiar in neurasthenia, psychasthenia, and hysteria, and include every admixture and degree of severity—exhaustion, fears, bad dreams, obsessional preoccupation, confusion, depression, somnambulism, amnesia, speech defects (stammering, stuttering, aphonia, mutism, verbal repetition), blindness, deafness, hyperesthesia, anesthesia, headache, tachycardia, tremors (fine, coarse, intention, or Parkinsonian), tics, peculiar gaits, paralysis (para-, mono-, and hemiplegia), and gaseous indigestion.

Average typical shell shock is rather different from ordinary civil neurasthenia or hysteria or the combination observed in civil traumatic neurosis, for in a typical syndrome the paramount symptoms are marked and variable tremor, hyperesthesia, especially auditory, paraplegic weakness, rapid pulse, speech defect, terrifying dreams, and apprehension.

Treatment.—Hydrotherapy, a cheerful atmosphere, optimistic suggestion, common sense explanation of symptoms, and diversion by means of occupational therapy are the chief reliances for cure.

Frederick Peterson.

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NEURASTHENIA

(*Psychasthenia*)

Definition.—Neurasthenia is a syndrome composed of numerous, rather characteristic physical and mental symptoms produced by fatigue of the nervous system.

Incidence.—It is fair to infer that more than one-third of the patients seen by neurologists in our large cities are neurasthenic or psychasthenic. Indeed, these conditions are probably even more common than this, for we know that large numbers of such individuals are treated by stomach specialists for gastro-intestinal symptoms, by cardiac specialists for palpitation and tachycardia, by genito-urinary specialists for frequent micturition, and by surgeons and gynecologists for the various pains and paresthesiæ that may exist almost anywhere in the body (spine, limbs, and pelvic organs).

It is of greatest importance that the general practitioner thoroughly understand neurasthenia, so that all sorts of technical procedures, including instrumental treatments and serious operations, will no longer be carried out on individuals whose symptoms so often yield readily to very simple treatment of the nerves.

Etiology.—Since neurasthenia is a neurosis of fatigue, it is acquired. Heredity may, it is true, account for easy fatigability of the nervous system, but the stress and strain of modern life, especially in cities, may overfatigue even the most sturdy and robust. Almost the entire urban population of this epoch is overstimulated and on the verge of neurasthenia. The weak succumb first, but the strongest often break under the strain.

While *overwork* and *worry*, which produce fatigue changes in the metabolism of the nervous system, are the chief causes of neurasthenia, any *physical disorder* that weakens the organism, any *poison*, like alcohol, that perverts the chemistry of nutrition, and any *enervating factor*, like excessive sexual indulgence, may be a major contributing factor in this type of nervous breakdown. Beard and many later writers have overemphasized the importance of the rôle of sexual indulgence. Anemia is a physical cause in a surprising number of cases and is probably to be considered one of the evidences of general malnutrition. Neurasthenia after typhoid fever, influenza, and other infectious and organic diseases, and after actual physical injuries (accidents) is not uncommon.

Morbid Physiology.—Since Beard published his noteworthy discussion of neurasthenia and psychasthenia over fifty years ago, little has been added to our knowledge of the pathology or symptomatology of the conditions. His conception of the pathology, "an impoverishment of the nerve force, resulting from bad nutrition of the nerve tissue," is really hardly more than restated in modern terms when we say that overwork and stress and strain induce fatigue neuroses by perverting the chemistry of metabolism in the nervous system. Countless papers and many books have been published to define and explain pathological fatigue, but without clarifying the problem. Ranke's idea of "fatigue products" has been accepted by many observers: Weichardt's theory of a "fatigue toxin," on the other hand, has been exploded by Lee. Perhaps the most satisfactory summary of the present knowledge of normal fatigue is that of Muscio. He thinks that "the term fatigue should be banished absolutely from precise scientific discussion, and consequently that attempts to obtain a fatigue test be abandoned." Any investigation of the effects of different kinds and amounts of work upon mental and physiological function, however, he believes to be valuable. Pathological fatigue is clearly quite a different problem which also involves change of function and of chemistry.

Symptoms.—Anxiety and anxious states which are so well marked in some forms of insanity seldom if ever develop in neurasthenia. Some degree of fear and worry can always be observed, but never real anxiety in the medical sense. Freud's summary of the Angst-neurose is a perfect description of ordinary neurasthenia or fear neurosis. There is no other disorder which produces such a multiplicity of symptoms, especially of the subjective physical type. The *mental symptoms* are few, but characteristic. The French have called neurasthenia "the malady of the little papers," because it is so common for neurasthenics to bring to the physician two, three, or more closely written pages which are catalogues of their complaints. This is done because the symptoms are numerous and so important to the patient that he fears to forget even a single one. While they are "ill-defined and motley," their typical association renders diagnosis especially easy. The following slightly classified list may clarify the conception of the syndrome:

Objective symptoms:

Fine tremor.
Palpitation, tachycardia.
Dilated pupils.
Hypertypical deep reflexes.
Suffusion of the conjunctivæ.

Subjective physical symptoms:

Feeling of general fatigue.
Gaseous indigestion.
Pain and paresthesia in any or many parts of the body, especially in the head and spine.
Feeling of frequent desire to urinate.
Feeling of tremor throughout the body.
Spots before the eyes.
Ringing or roaring in the ears.
Vertigo.

Mental symptoms:

A general undercurrent of apprehension in all cases, very pronounced in some, as fears, phobias, panics.
Difficult concentration.
Troubled sleep or insomnia.
Irritability.
Imperative thoughts or obsessions.

This condensation of the chief symptoms of neurasthenia is brief, but elaboration by the patient of the details and variations under each item is one of the symptoms in itself and lengthens the catalogue interminably. Not all of these symptoms are present in every patient, and emphasis is laid on different manifestations in each individual. Usually, however, the term "*neurasthenia*" describes cases in which the physical symptoms, objective and subjective, predominate; the term "*psychasthenia*," those in which the mental symptoms predominate over the physical symptoms. Naturally, no two cases are exactly alike. The symptoms are very similar in all, but are colored by the character and temperament of the individual. They are also modified by any marked neuropathic or psychopathic predisposition, and by any hysterical, melancholic, or hypochondriacal tendency.

Neurasthenic Symptoms.—The *fine tremor* is almost always noticed in the extended fingers, and sometimes in the lips, face, and tongue. Patients often complain of feeling an "inward tremor" all through the trunk of the body. Occasionally this is accentuated by what is called "throbbing arteries," a condition no doubt associated with the palpitation and general vasomotor disturbances.

Neurasthenic *tachycardia* is often a most distressing symptom associated with palpitation, irregularity, and rapid action of the heart and feelings of oppression in the chest. It is sometimes quite similar to that of hyperthyroidism. Its relation to a possible increase in the thyroid secretion in neurasthenia is not yet proved.

When there is much cardiac disturbance in neurasthenia there is also apt to be *gaseous indigestion*. It seems as if the tenth pair of nerves were often about the first to feel the effects of the fatigue neurosis. Palpitation and gaseous indigestion are very frequently the chief complaints of the patient, and are many times treated for long periods before their real nature is discovered. The indigestion of the neurasthenic is characterized chiefly by the formation of gas, atony of the musculature, slow and defective digestion, and occasionally by variations in the amount of hydrochloric acid secreted. The gas is probably formed by the epithelial cells, and is certainly not swallowed air or a product of decomposition of food. While the stomach alone is ordinarily affected in neurasthenia, evidence of

atony can at times be found in the intestines, with gas-formation and alternating constipation and diarrhea.

The feeling of *general fatigue* is manifest in the lack of ability to carry out much muscular effort. The patients tire easily in walking or standing, and are quickly exhausted by active occupations.

Pain and paresthesiæ are among the common symptoms. Headaches figure prominently in every list handed in by the patient. They may be moderate or severe, and in any part of the head, although they are usually occipital. With the headache there is often a sense of constriction, as if a band were tied about the head. This is so common as to be known as the "*helmet sensation*." Pain in the back of the neck and down the spine has been given the name "spinal neurasthenia." It may radiate down the loins and legs, and be associated with tenderness of the spine to deep and superficial pressure in certain spots, or down the entire length. There may also be shifting temporary pains in almost any part of the trunk or extremities. With the pain there is associated every variety of perverted sensation, pressure, for instance, and tightness, tingling, prickling, numbness, stretching, constriction, soreness, stiffness, heat, cold, etc.

Frequent micturition, probably due to weakness and irritability of the bladder, is so frequent a neurasthenic symptom that it should be especially remembered as such, lest it receive useless if not disastrous local therapy, when only general treatment of the nerves is required to bring about cure. This nervous irritability is apt to be more marked at night than during the day.

The fatigue symptoms are often noted in some of the nerves of special sense. A very frequent complaint is of *muscæ volitantes* ("spots before the eyes") and of *tinnitus aurium* (ringing or roaring in the ears). Peculiar tastes and smells have been observed.

Vertigo is a rarer symptom, but occasionally a prominent or even a chief manifestation.

The *deep reflexes* are usually much increased (hypertypical), sometimes to an easily exhaustible clonus, or pseudoclonus.

To this general catalogue of objective and subjective physical symptoms should be added *dilatation of the pupils*, hypermobility of the pupils, and sometimes a varying irregularity; neurasthenic asthenopia and such general symptoms of optic exhaustion as weakness of the muscles, easy fatigue of accommodation and of the retina, and sometimes moderate or marked photophobia. Congestion of the conjunctiva is frequently seen: it is included in a rather large list of vasomotor disorders such as localized flushing, sweats, and coldness and clamminess of the hands and feet.

It is usual to find more or less *anemia* and some disorder of the *urinary secretion* as evidence of altered metabolism. The urine is often scanty and high-colored, and the content of phosphates, oxalates, uric acid, and urates is apt to be high.

Psychasthenic Symptoms.—The above features, together with the general apprehension, are characteristic of neurasthenia proper. When the mental symptoms, especially *fear*, dominate the syndrome the condition is more correctly called psychasthenia. In this, the physical symptoms do not occupy the consciousness to so great an extent because the fears are so prominent. With the fears are associated feelings of mental weakness, inability to concentrate, and incapability of mental effort. Attempts to

read, think, or converse tire the mind, and a patient begins to believe his memory is failing, because of the difficulty of recollection. This mental fatigue leads to hypochondriacal introspection which, in turn, increases the fears and depression. Naturally, therefore, the most common of all special fears is that of going insane; this is based on the mental distress just described, plus the various pains and paresthesias in the head. Next most common is perhaps the fear of falling down unconscious or dying: this is very probably produced by the prominent vertiginous feelings, palpitation, and the sense of oppression in the chest. There may be as many manifestations of fear in psychasthenia as there are possible fears in the world. It is not very clear how any special type is determined. The origin sometimes can be reasonably explained; but again, the fear seems like some fragment of a nightmare which appears suddenly from the subconscious and forces itself as an imperative thought or obsession into the consciousness. To some of the more usual manifestations special names have been given: agoraphobia (the fear of open spaces), claustrophobia (the fear of closed spaces), monophobia (the fear of being alone), anthrophobia (the fear of people), pathophobia (the fear of disease), mysophobia (the fear of contamination), astrophobia (the fear of lightning), phobophobia (the fear of fears), and pantophobia (the fear of everything). Some day perhaps we may be able to untangle from the subconscious mind the determinant of any particular fear, but so far efforts to do this by psycho-analysis have proved unfruitful.

The psychasthenic individual practically always has good insight into his mental condition, recognizes the incongruity of his fears, and laughs at their folly while he describes them. They force themselves upon him nevertheless, and although he yields to them he is usually careful to keep from his friends or relatives any inkling of their existence. Knowing that others will criticize or be amused, he is careful to conceal the fact that he constantly washes his hands, or door-knobs, chairs, and towels when he fears contamination, that he fears to go anywhere alone, and that he is afraid to cross streets or go into a street car or theater. The fears seem foolish to his friends, but they are constant and often exquisite torture to the patient. They often lead to real panics, with such physical disturbances as trembling, pallor, gasping, oppression in the chest, and palpitation.

It must be remembered that fear in itself is a normal physiological reaction, which varies in degree in different individuals. Like pain it makes for caution and self-preservation. It may be very marked without being pathological, especially when it is excited by some definite event or circumstances. In the neurasthenic and psychasthenic it is not only excessive in proportion to the causative factors, but is usually recognized by the patient as unreasonable and evoked by trivial causes. Whatever conditions underlie the fatigue processes in the nervous system, they always bring about timidity and apprehension in even mild neurasthenia, and torturing and abject fears in severe psychasthenia.

When general or special fears force themselves uncontrollably into consciousness, despite their rejection by reason, they in a way possess or obsess the mind and may be considered obsessions or imperative ideas. In psychasthenia other conceptions or thoughts may also take possession of the mind and inflict the same kind of haunting torture, for the patient is unable to substitute a normal train of thought or another idea for the

obsession. Nevertheless it inflicts suffering. The ideas, words, phrases, and tunes, that may thus enter the consciousness, are as varied as the world of thought. One patient was harassed for several years with a fear of going into any house or hotel where there might be a canary bird. The fear was that as the birds are fed on canary seed this might be blown about, get on her food, be swallowed, and grow in her stomach. She saw the complete nonsense of the fear, and was covered with shame in telling the story. Yet the panic was very real at the sight of a canary, and the torture of the obsession itself extreme. Very many patients fear to see sharp instruments lying about (scissors, knives, hat-pins) lest they might seize one and run it into someone. However strong the obsession, patients have never, in the author's experience, actually attempted to follow the impulse, which is less an impulse than a fear of an impulse. Another rather common obsession, which is particularly trying to some delicate-minded women or to a clergyman, is the fear of saying some profane or obscene word. The obsession may be visual, a forced presentation in consciousness of some obscene image or scene at the most inappropriate time, for instance during prayers or while preaching a sermon. This has led some patients to believe themselves actually victims of "demoniacal possession."

The author feels inclined to limit the term "psychasthenia" to cases of this kind in which fear is the dominant psychic condition, and to cases in which the fear is also associated more or less with such obsessions as the fear of saying or doing a wrong or improper thing, or of insanity as a result of lack of control of the thoughts. Janet has included under psychasthenia, inebriety, sexual perversions, certain deliria, *folie du doute*, and certain types of criminality, which seem to form another category of psychopathic conditions on the borderland of insanity. Some of them may at times be psychasthenic, but the greater majority are not to be included among the fatigue neuroses.

Sleep is usually imperfect in both neurasthenia and psychasthenia, and directly in proportion to the severity of the neurosis. Even when insomnia is marked it is not obstinate and usually yields to mild therapeutic measures. Patients complain usually of light, restless, unrefreshing sleep from which they wake up tired and exhausted in the morning.

Diagnosis.—The number and variety and the peculiar association of certain characteristic symptoms should render diagnosis of neurasthenia easy; psychasthenia also has its own peculiar mental ear-marks. Naturally the whole body should be examined thoroughly for any real organic disease which may exist as a cause or complication. *Hysteria*, which sometimes exists simultaneously, has its special stigmata in the way of paralyses, spasmodic disorders, and anesthesias. Sometimes, though rarely, *paresis* may begin like neurasthenia, but the routine general examination demonstrates by objective symptoms (pupils, deep reflexes, speech or writing, or the serology) the presence of the more serious disease.

Course and Prognosis.—Both neurasthenia and psychasthenia are chronic conditions. They begin slowly and usually do not send the patient to the physician for many months after onset. Because of misinterpretation of the many symptoms, correct diagnosis is often not made for a year or two. As soon as the condition is recognized it can usually be cured within a few months. Psychasthenia, which is the more severe type of fatigue neurosis, tends to last longer than neurasthenia, but all cases are

curable under proper conditions. There is considerable fluctuation of symptoms, and recovery is not uniformly rapid, but rather a rhythmical progress which is quite characteristic of most nervous disorders. After recovery similar causative factors may easily bring about a recurrence of the disorder. Insanity as a result of a fatigue neurosis is almost negligible it is so rare. When it occurs there is a psychopathic constitution, and the neurasthenic or psychasthenic state is only a phase in the evolution of a psychosis.

Treatment.—The fundamental purpose in the treatment of neurasthenia and psychasthenia is to *improve the nutrition* of the nervous system. A gain in weight, which is evidence of improvement in the general nutrition of the body, is an actual index of the beginning of recovery. While Weir Mitchell in his little book on "Fat and Blood" stressed *rest* as the chief element in the cure of this condition, he emphasized the importance of special nutrition at a time when the vitamins were not even guessed at, and curiously enough relied chiefly on the foods we now know to be so rich in vitamins (milk and cod-liver oil). Rest has been found to be comparatively unimportant and the rest-cure has long been abandoned in these cases. The overfeeding that used to be practiced is rarely, if ever, necessary. As a rule, it is sufficient to add to any general diet merely a glass of milk at each meal, three pats of butter at each meal, and a considerable quantity of leafy vegetable once a day (lettuce, beet-tops, spinach, etc.). These foods are so rich in vitamins that they soon stimulate the whole chemistry of the body. As most patients have at least moderate anemia, *iron* ought to be given—preferably in the form of an albuminate or peptonate. At one time there was an inclination to ridicule the administration of *phosphorus* to these nervous patients, but experience has shown that certain glycerophosphates are of very great value in nerve chemistry, and that 20 grains of sodium glycerophosphate should be added to the diet at each meal. It was given to hundreds of thousands of German workmen and soldiers during the Great War. When gaseous indigestion is a prominent symptom, administration of the dose in a full glass of hot water half an hour or an hour before meals seems to double its efficiency.

It is needless to say that any *concomitant physical disorder* should not be overlooked. The whole individual is to be treated, and this includes both body and mind. Some cults and some physicians have tended to treat the mind alone, and most physicians, with their natural bent to the objective and material, have been inclined to treat the body alone, and to seek some particular physical cause or some focus of infection, which might explain the multitude of symptoms, while they neglect what is usually the only important physical symptom, the disorder of metabolism.

The next valuable therapeutic measure is change—change of scene, change of environment, change of climate, and change of occupation, to get the individual out of the ruts in which the disorder has developed. Its tonic value to both body and mind cannot be too strongly emphasized. Perhaps this, next to overfeeding, was the secret of the success of Weir Mitchell. He provided a new environment, new faces, new interests, novel surroundings, and change of climate to those who came to him from far. The beneficial effect is quite proportionate to the amount of change. Marked changes are not always possible for people of moderate circumstances who must continue their daily occupations, but even for them some change

from the daily routine can be devised—outings in a new direction, and the cultivation of some new interest or avocation. This is part of the psychotherapy, the main feature of which is a careful, reasoned explanation to the patient of the origin of the neurosis in fatigue and malnutrition of the nervous system, and of the baselessness of his fears and obsessions, with constantly reiterated suggestions as to certainty of cure. Suggestion is very powerful in neurasthenia and psychasthenia and directly in proportion to the faith of the patient in the physician. The physician whose personality inspires confidence, and who has common sense and sympathetic understanding, is most successful in psychic treatment.

A word should be said as a *warning against psycho-analysis* in these conditions. The tendency to pay too much attention to the physiological processes that go on in the body may lead to hypochondriasis; and a meticulous self-inspection of the mental processes, fears, obsessions, dreams, trends, and desires is far more dangerous.

Hydrotherapy is useful for tonic treatment (spinal douches) and for marked insomnia (the wet pack). For ordinary insomnia, and for restless irritability and nervous tension, the simplest, least harmful, and most satisfactory *sedative* is one of the bromids.

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VASOMOTOR AND TROPHIC DISORDERS

The numerous vasomotor trophic disorders affect with varying severity the normal activity and nourishment of the skin, subcutaneous tissues, sweat and sebaceous glands, blood-vessels, bones, muscles, and nerves, all of which are supplied with blood-vessels and subject to trophic control by the involuntary nervous system. Probably all these diseases depend on some disturbance in the sympathetic system, between its origin in the subthalamic region of the central nervous system and its endings in the different structures. This view is supported by the fact that diseases of the central nervous system are not infrequently associated with vasomotor trophic disorders. Why some structures are not affected in certain conditions is not known. The close relation of the disturbances is clearly shown by the overlapping of the signs and symptoms. Any part of the body, even internal organs, may be involved as the symptoms referable to the heart, brain and spinal cord, lungs, gastro-intestinal tract, and genito-urinary tract demonstrate. The conditions are often congenital or hereditary, and are often seen in neurotic individuals. The pathology is very little understood. The treatment is almost always unsatisfactory. Sometimes attacks cease to recur spontaneously, but this, the only type of recovery, cannot be foretold and is not usual. Patients do not die from the disease, except from the rare angioneurotic edema of the glottis.

Raynaud's disease is a neurovascular disorder which affects the fingers, toes, and occasionally the nose, ears, chin, lips, and nates. It is usually symmetrical. The condition was first described by Raynaud in 1862. Of the many notable works on the subject which have appeared since that time that of Cassirer is the most comprehensive.

Incidence.—The disease is not common. It may be associated with such other nervous diseases as tabes dorsalis, syringomyelia, multiple sclerosis, epilepsy, and migraine, as well as with other diseases of the same group like erythromelalgia, angioneurotic edema, acroparesthesia, and scleroderma. It has been said to accompany all common infections. In malaria, thrombosis of the small vessels may occur. Women are more often affected than men. The incidence is highest in individuals between twenty and fifty years of age.

Etiology.—Except for the fact that the disease is produced by some factor which involves the vasomotor nerves or their centers, the etiology is unknown.

Morbid Anatomy.—The reports of changes in the nervous system are contradictory. The lesions themselves seem to consist of a change in the capillaries, which renders them more tortuous and sluggish than normal.

Symptoms.—The disease begins suddenly, and in the vast majority of cases symmetrically. It passes through three stages: local syncope; local asphyxia; and local gangrene. In the *first stage* there is a feeling of deadness, severe pain, or paresthesia in the parts affected. Vasoconstriction renders them pale and cold. The temperature of the skin is low. This attack may disappear for minutes, hours, or longer, and only recur as a similar attack, or it may be followed by the *second stage* (local asphyxia). In this, the parts affected become dark blue or black. The pain is intense. Blisters may form, but there is never bleeding from the skin. In some cases this stage resembles erythromelalgia, with its swelling, deep-red coloration, and intense pain. It may persist for weeks or months, before the *third stage* ensues. Parts may then drop off. Local infection is rare. The disease may begin with the second stage.

The pain is often associated with sweating. Sensation is much diminished in the affected areas. Muscular atrophy is rare. The nails are severely affected, and involvement of the bones causes sclerodactylia. This may be demonstrated by *x*-ray photographs.

Mild Raynaud's disease, not severe enough to send the patient to a hospital, is not very uncommon in private practice.

Complications are many; paroxysmal albuminuria; hemoglobinuria; gastric disorders; and intermittent occlusion of cerebral vessels which produces various syndromes, such as aphasia, epilepsy, and paralysis.

Prognosis.—The prognosis is not usually favorable. Although one attack may be all that the patient may have this is not certain. The attacks may recur for years.

Diagnosis.—Differential diagnosis is not difficult except when the disease is atypical and resembles the other conditions already mentioned. *Endarteritis obliterans* and *ergot poisoning* must also be distinguished. The former may be differentiated by the involvement of the lower extremities, asymmetry, absence of pulse in the dorsalis pedis, and the almost exclusive (95 per cent. Buerger) occurrence in Polish, Russian, or Galician Hebrews. In ergotism the history suffices.

Treatment.—The treatment is not very satisfactory. It consists of administration of thyroid, local application of heat, massage, and general upbuilding. The Leriche operation may be tried.

Hereditary trophedema is manifested by chronic edema of one or both legs, one or both arms, or the face. It may affect but a part of an extremity. The condition is hereditary, often congenital, and extremely rare. In ten years not one case was admitted to Bellevue Hospital. It affects women more frequently than men, and appears in the decade after puberty.

The *cause* is not known. The characteristic symptom is a great swelling of the affected parts, which either pit but slightly or not at all. The skin is much thickened. There is no pain or tenderness. The discomfort results entirely from the deformity (swelling).

Diagnosis is not difficult. Complete or nearly complete absence of pitting upon pressure serves to differentiate the condition from cardiorenal edema. Progressive lipodystrophy is ruled out by absence of the characteristic distribution of fat, and by the absence of lipomatous atrophy above the waist-line.

The *prognosis* is not favorable. No *treatment* is of advantage. The disease is incurable, but does not cause death.

Erythromelalgia is characterized by redness, swelling, and painfulness of the hands or feet, or both. The disease is rare. It occurred but fifteen times in about 400,000 admissions to Bellevue Hospital in ten years. *Pain* is usually the first symptom. This affects, as a rule, the ends of the toes or fingers. Redness, which may be very intense, appears later and is followed by swelling. A pendent position and heat aggravate the symptoms, cold and the supine position diminish them. Headache, dizziness, tachycardia, palpitation, and syncope are very often associated. The disease may be associated with signs or symptoms of Raynaud's disease, angioneurotic edema, acrocyanosis, or scleroderma. It may last for years, and is not dangerous to life. There is no effective *treatment*.

Causalgia is a painful condition of the hands or feet due to irritation of a nerve by injury. Associated with the pain are glossiness of the skin, swelling, redness, trophic changes of the nails, and sweating. The slightest stimulus, physical or mental, brings a paroxysm of pain. The condition was fairly common during the World War, but is rarely seen in civil life.

The underlying *cause* is a disorder of the sympathetic fibers of the injured nerve. The disease affects the nerves of the arm in the following order of frequency: median, ulnar, and radial; those of the leg as follows: internal popliteal, external popliteal.

Scars and foreign bodies about the nerves should be removed. A Leriche operation, *i. e.*, stripping off the sympathetic fibers, may help. The *prognosis* is usually poor.

Chronic progressive hypertrophic acrocyanosis is a very rare disease in which the soft parts of the hands or feet hypertrophy. The areas involved become cyanotic or intensely red. Bones are not affected. The slow progressive character of the condition differentiates it from Raynaud's disease and the lack of pain from erythromelalgia. It must not be confused with acromegaly.

Acroparesthesia is a subjective sensory disorder of the fingers which has been known for many years. The patients feel tingling, and have a

sensation of "pins and needles" or formication in the finger-tips. The condition is seen not infrequently. It occurs almost always in females over thirty, and is often associated with disorders of the ovaries. Various diseases of the spinal cord have also been found in acroparesthetic patients, *e. g.*, tabes dorsalis, tumor, syphilis, multiple sclerosis, and syringomyelia. Acroparesthesia may be the first symptom of Raynaud's disease. It is a disease of the involuntary nervous system which may be due to disease of its centers in the spinal cord or to more general conditions of endocrine origin. The *cause* is believed to be vasoconstriction of the vessels to the distal nerves.

Symptoms.—The condition, which is almost always bilateral, may begin slowly or suddenly. Plunging the hands in icy water may be the immediate cause. It is worse during the night and in the morning, as a rule. In some cases the skin looks blanched. Very slight hypo-esthesia may be found over the finger-tips. Pain is rare.

The disease is *chronic*, but disappears, as a rule, in later life. It does not lead to death. It is easily diagnosed, either as a symptom or as a disease.

The *treatment* consists of administration of general tonics, such as arsenic and iron, and faradization of the affected parts. When definitely associated with ovarian disorder corpus luteum may be given.

Multiple subcutaneous gangrene is closely allied to Raynaud's disease in which multiple areas of gangrene occur. It develops in hysterical or neurotic individuals. In some cases it is self-inflicted, but in others it is definitely of organic origin. If the skin is intact over the subcutaneous gangrene self-infliction of the condition can be ruled out.

The disease usually occurs in women under forty. Frequently a local trauma such as a burn or pricking by a needle has preceded it by months or years. Pain and paresthesia often develop before the gangrene. The infected areas are of various size and may be anywhere on the skin or mucous membranes. They may coalesce. The disease may recur frequently or become progressive, spreading widely. It sometimes lasts for years, but is not fatal. The *treatment* of the organic type is unsatisfactory. In the self-inflicted type psychotherapy must be used.

Scleroderma is a disease of the skin characterized principally by pigmentary disorders, thickening, and atrophy. It is often combined with sclerodactylia. It is not common, only 8 cases being found in the 400,000 admitted to Bellevue Hospital in ten years. Women are more frequently affected than men. The condition may develop at any age. The *cause* is a disorder of the involuntary nervous system the precise nature of which is not known.

Symptoms.—The manifestations are extremely variable. Increase or decrease of pigment, thickening and atrophy of the skin, loss of subcutaneous fat, disorders of sweating, and cyanosis or blanching may appear. All of these are sometimes preceded by diffuse swelling. The muscles may be atrophied in either the extremities, trunk, face, or tongue. Joints and tendons may be affected. If the disease causes atrophy of the bones of the fingers, sclerodactylia develops. In brief, any of the structures of an extremity except its nerves may be involved. Whether viscera are affected by sclerosis is still unsettled. The distribution is usually spotty, but may be quite diffusely distributed, and is usually bilateral. The face, neck, and shoulders are most often involved, the trunk and legs more

rarely. The skin of the whole body is sometimes diseased. The subcutaneous tissues may atrophy and become rigid, and the subcutaneous fat disappear. If one-half of the face is so affected, the picture is that of progressive facial hemiatrophy. The condition is often found where there has been pressure (garters).

In some cases the syndromes of Raynaud's disease or erythromelalgia appear entirely or in part.

Various nervous diseases may be associated with scleroderma, such as tabes dorsalis, brain tumor, paralysis agitans, dystonia musculorum deformans, and epilepsy. The simultaneous occurrence of Graves' disease, however, is too common to be a mere coincidence.

Diagnosis.—The disease is not hard to diagnose. It must be differentiated from Addison's disease, *argyria*, and *dermatomyositis*.

Prognosis.—The prognosis is poor. The disease progresses either steadily or by remission. The limitation of motion of the mouth, head, and fingers may be very great indeed. Gradually the patient weakens and dies of some intercurrent, acute malady.

Treatment.—The treatment is unsatisfactory, as a rule. Thyroid extracts may be of assistance. Local salves have no permanent beneficial effect.

Progressive facial atrophy is wasting of the fat of the face, usually unilateral. This is associated with thinning of the skin and depigmentation or abnormal pigmentation (brown, yellow, bluish). The muscles and bones may also be affected. The disease is extremely rare.

Etiology.—The cause is still obscure, but is in all probability a disorder of the involuntary nervous fibers in the head region or of the central nervous system. The distribution of the disease is certainly that of the sympathetic supply to the head region and not that of any cranial nerve.

Symptoms.—The disease usually begins before thirty. It is found equally in both sexes. It may begin about the orbit, the cheek, or the lower jaw. The masticator and tongue muscles may be affected as well as those of the face (N. VII). This involvement does not interfere with muscle function, and there is no reaction of degeneration on electrical testing. The eyelashes may fall out or become gray. The pigment of the skin becomes either brown or yellow or disappears. Pain (neuralgia) is often present. The atrophy may remain limited to one-half of the face, but not always. Further hemiatrophy of the same type affecting the entire body may occur. It is often associated with disorders of the sympathetic system, and is closely allied to scleroderma—indeed, Cassirer regards it as a form of this disease.

The disease may only involve the subcutaneous fat, and thus resemble progressive lipodystrophy.

Diagnosis.—The diagnosis is not difficult in clearly defined cases. When only pigmentation changes and cutaneous atrophy are present *scleroderma* is hard to differentiate. Cases with loss of subcutaneous fat only are easily differentiated from *progressive lipodystrophy*.

Prognosis.—The disease, as a rule, is progressive for a considerable period after it is first observed. It then reaches a standstill. It does not cause death.

Treatment.—There is no beneficial treatment. Removal of the superior cervical ganglion has been attempted.

Facial hemihypertrophy is an extremely rare disease in which there is unilateral hypertrophy of the skin, muscles, and bones of the face. It is slowly progressive, but finally comes to a standstill. There is no *treatment*. The *diagnosis* is best made by *x*-ray of the skull.

Progressive lipodystrophy is a disorder of the subcutaneous fat in which there is atrophy above the waist-line and hypertrophy below it. Not more than 50 cases have ever been reported. Both men and women are affected. The *cause* is unknown.

Symptoms.—There are no symptoms or signs except the disorder of fat distribution. The face is involved, as a rule. Below the waist-line there is accumulation of fat in large masses over the buttocks, inguinal regions, inner aspects of the knee and the lower legs. Pitting is either slight or absent. The disease begins usually in the second or third decade, and progresses very slowly for a period of years. It usually becomes arrested in adult life. The condition is not fatal, and appears to have no ill effects whatsoever. One patient seen by the writer passed through a pregnancy quite normally.

Diagnosis is not difficult. The disease may be confused with the *trophedema of Meige*, but the atrophy in the upper parts of the body and the fact that the changes are bilateral are diagnostic.

Treatment.—No treatment has served to alter the condition.

Walter M. Kraus.

Mental Disorders

Introduction.—Few disorders are so sadly neglected by the medical profession as mental disorders; in regard to them the general practitioner frequently assumes an air of complete detachment, and does not hesitate to admit his ignorance of their mechanisms, their classification, their treatment. Psychiatry is apt to be considered a dubious blend of scientific and metaphysical formulations. Owing to the special emotion associated with the term *mental*, many mental disorders are euphemistically referred to as *nervous* disorders. It is important to realize that few cases of "nervousness" or "nervous disorder" are not intimately related to instinctive and emotional problems, and therefore, cannot frankly be called *mental disturbances*. A large group of ailments, the psychoneuroses, are based on emotional conditions, and are traditionally separated from the more severe mental disorders; these might well be classed as *minor psychoses*. The mechanisms which are important in evoking both the major and minor mental abnormalities are also at work in the adjustments of daily life, and are more important in the etiology of sickness in general than is usually realized. Invalidism often depends to a large extent on the personality of the patient, his situation, and his problems. These may require as much attention and as skilled analysis and treatment as any localized lesion or abstract disease. It is becoming more and more clear that in addition to specific noxæ and

disease processes, the personality of the individual, the original endowment, the life experiences, and the immediate degree of stress and strain must be studied. Investigation of specific organismal noxæ is simple in comparison with the study of immunity to the demands of the social environment. To comprehend the symptoms of mental disorders it is essential to understand the more complex mechanisms of human nature, for such disorders are merely an expression of the functioning under difficulty of these complex psychologic mechanisms. The physician must have, in addition to an adequate grasp of general medicine and neurology, a good knowledge of the instinctive life, of the conditioning of the instincts by experience, of the rôle played by pleasure in fixing modes of behavior, of the contrast between logical and autistic or undirected thought. Neurology relates the mass reflex to a more primitive stage of reflex organization, and the sign of Babinski to the infantile type of plantar reflex; so in civilized man modes of thought and behavior can be traced to the primitive mentality of savage ancestors, and the morbid behavior and thought of the adult may find their explanation in infantile tendencies.

The Minor Psychoses (*Psychoneuroses*).—In this group of mental disorders the symptoms do not appear to be closely related to the central part of the personality; the mutual understanding of the patient with his fellows is not seriously disturbed, for he does not view the world through a discolored or distorted medium as in the major psychoses.

The symptoms include such disturbances as headache, vomiting, paralysis, blindness, attacks of various types (hysteria, conversion-hysteria), morbid fears (phobias), compulsive thoughts or acts (obsessions). The causes lie in the instinctive and emotional life, and cannot be formulated in terms of physiology and biochemistry; they can only be made clear by a thorough investigation of the complex psychologic situation. That these minor psychoses are not so sharply differentiated from the major psychoses as is generally thought is evidenced by the fact that patients with obsessive thoughts may at times develop delusions of persecution.

Conditions of Distorted Personality.—The individuals in this group are not usually recognized as patients; their personality and social attitude are seldom scrutinized from the psychiatric standpoint. The personality may be handicapped by undue shyness, compensatory aggressiveness, ill-balanced enthusiasms and prejudices, serious maladjustment to the demands of the domestic, social, industrial, or professional environment. These conditions are sufficiently numerous to represent a serious social loss. Such disturbances of personality receive little relief from the general practitioner. The patients do not realize that they need help, and even if they do, the general practitioner is usually unable to give it.

Symptomatic Psychoses (*Mental Symptoms in Somatic Ailments*).—The symptomatic psychoses are the psychologic changes associated with or elicited by physical ailments. The first indication of a physical ailment may be a change of mood, a feeling of lack of energy or ambition, a depression perhaps colored with remorse, anxiety, or suspicion. Undigested memories, crude trends, repressed loves and hates normally hidden may come to the surface under the disturbing influence of a focal infection, a metabolic or endocrine disorder. Whenever mental symptoms of any nature develop, thorough physical examination is desirable.

In children, irritability or emotional instability may be the earliest in-

dication of chorea. In *cardiorenal* and *pulmonary disorders* transitory confusion and alteration of mood are familiar; occasionally the waves of depression, suspicion, and misinterpretation are associated with special hallucinations which may be in part due to visual after-images. *Hepatic disorders* are frequently accompanied by depression and this receives somewhat undue recognition in the term "melancholia." In *pernicious anemia* the patient may develop misinterpretations and have fantastic experiences which are chiefly nocturnal, but which may not be corrected in the day time. The mental disturbance of *pellagra,* which is one of the three fundamental symptoms of the disease, varies from emotional instability resembling hysteria to profound agitated depression and permanent impairment of the intellect. In the terminal stages of disease with impaired nutrition of the brain, mental symptoms occur with few exceptions. *Febrile disorders* are particularly liable to cause psychologic variations. In infections and the complicated physical changes of the *puerperium* the first indication of mental disorder may be change of mood accompanied or followed by slight difficulty in grasping complex data. As the mental involvement increases, even simple perception suffers; words may not be accurately grasped nor objects seen clearly. Still later the patient hears and responds to imaginary voices, sees terrifying faces, reaches for imaginary objects, and, less commonly, has hallucinations of smell, taste, or touch. At the same time the orderly utilization of past experience is disturbed. The patient may know neither where he is nor what the date is. Mental confusion, especially if it is accompanied by hallucinations, is usually called delirium. The degree of confusion may vary, and the condition may be intermittent or continuous. It is most marked at night and least obvious during the day. In some cases the symptoms do not develop until after the febrile crisis has passed and the temperature has returned to normal.

In the mental disorders accompanying infectious diseases the manifestations may be much more complicated than in the simple delirium described. They may resemble the symptoms of other psychoses and it may be difficult to distinguish the toxic symptoms from those due to the psychologic instability of the patient. Boastful talkativeness with flight of ideas may be the result of infection in a patient with a constitutional tendency toward marked alternation of mood (manic-depressive constitution); or bizarre, fantastic ideas, odd symbolism or the presence of fragments of childish and primitive behavior may suggest that the individual is predisposed to deviations from normal which are more marked than those associated with the manic-depressive type of personality. Muteness and lack of co-operation may be due to a desire to withdraw from reality as well as to circulating toxins. Removal of normal inhibitions through the underlying somatic ailment may reveal the true nature of the personal equilibrium and permit the physician, after the immediate disturbance is cured, to deal adequately with the personal problems thus disclosed. In the psychoses of pregnancy and childbirth the psychologic significance of the approaching and possibly fatal ordeal, the sense of being unworthy to produce a new life, and the possible resentment of such reinforcement of the marital bond are apt to be ignored, while the attention is focused on the non-protein nitrogen content of the blood or on the immunity of the patient.

Prognosis.—The prognosis depends on the nature and severity of the

physical disturbance and the reaction of the tissues and, in addition, on complicated psychologic factors.

Treatment.—The treatment of symptomatic psychoses is primarily that of the somatic disorder. For excitement, the continuous warm bath is desirable because it allays the symptoms without the use of sedatives and hypnotics. Since refusal of food and liquid increases the existing mental disturbance, the nutrition of the patient must be carefully watched and food administered by the nasal tube whenever necessary.

Psychoses Due to Organic Disease of the Brain.—Of the psychoses caused by organic disease of the brain the most familiar are due to syphilis; others are produced by cerebral arteriosclerosis, brain tumor, epidemic encephalitis, senile degeneration, and epilepsy. Since the mental abnormalities which are symptoms of cerebral lesions may precede by a considerable interval the appearance of symptoms which reveal the nature and localization of the organic change, they are not infrequently at first considered functional or hysterical. The earliest manifestation may be a blunting of the fine edge of the personality with loss of the delicate appreciation of social and ethical values; a strange utterance which cannot be explained by the relatives; or slight transitory difficulties of memory or of comprehension of a total situation. There may be mild transitory disorientation, a tendency to forget recent occurrences, pseudoreminiscence. All these evidences of mild intellectual impairment are common to the various types of organic psychoses, but, as the lesion develops and the neurologic symptoms become prominent, each organic brain disease tends to show its own characteristic mental syndrome.

Brain Syphilis.—The clinical picture due to syphilitic disease of the brain may in part be determined by the type of reaction of the patient. This may, in part, account for the great variations in the clinical picture of *general paralysis*, in which manic, depressive, schizophrenic, and hallucinatory syndromes are found. These variations are mainly of theoretical interest, as the disease eventually wipes out all individual traits.

Cerebral Arteriosclerosis.—The familiar early symptoms of cerebral arteriosclerosis are headache, dizziness, ringing in the ears, mental fatigue, and the effort required in remembering. Later, general reduction of intellect with special impairment of memory ensues. The development of additional symptoms depends on the extent and position of the anatomic lesion. The well marked symptoms of the late stages may explain early manifestations. For instance, hemianopia may be preceded by extraordinarily vivid, visual hallucinations. The emotional lability, seen so often, is closely related to the spasmodic laughter and crying of the psuedobulbar syndrome.

Senility.—Senile changes in the cortex of the brain are apt to be accompanied by impairment of memory for the recent past, inability to receive and retain new impressions, pseudoreminiscence and change in personality. The patient is apt to be disoriented and to live in the past. Lability of mood is common; tearfulness and cheerfulness alternate rapidly. Even before the memory is impaired the temper may be less controlled than normal, and the patient may become unusually egotistical, imperious, and suspicious. As this type of individual often refuses to give up authority, he may form a storm center in the home while in hospital he is quite placid. Some senile individuals become so suspicious that they

accuse those around them of stealing objects which they themselves have mislaid; they may hear robbers prowling about the house at night or have a transitory delirium accompanied by fear.

Brain Tumor.—The mental symptoms associated with tumor of the brain vary with the location, character, and rate of growth of the neoplasm. In many instances the intellect is involved, the patient shows dulness and confusion; periods of excitement may occur. Not uncommonly the mental symptoms change; comparative mental clearness and alertness alternate with confusion. The intellectual functions become more and more involved as intracranial pressure increases. The incidental delusions and peculiarities of behavior are, as a rule, but an inconspicuous part of the syndrome. Mild euphoria is common, and is not limited to tumors of the frontal lobe.

Epidemic Encephalitis.—In the acute stage of the encephalitis the mental symptoms may be those of a toxic delirium, or a talkative excitement without the exhilaration or distraction of manic excitement, or a more or less profound stupor. In the chronic stage, even when there is no demonstrable Parkinsonian syndrome, the patient may find great difficulty in initiating new activities and in maintaining alert attention and easy adaptation. This is not secondary to a change of mood, but is closely related to the disorder of motility peculiar to encephalitis. The sense of inadequacy to translate wishes into deeds often curbs any inclination to make plans or show initiative. In childhood the personality as well as the intellect may undergo striking change. After an attack of epidemic encephalitis a previously well-behaved child may become very disorderly, develop simple or complicated motor tics, may lie, steal, or misconduct himself sexually. The change in personality, such as increased irritability and lessened adaptability, which encephalitis produces in adolescence, may be fully recognized by the patient. The adult personality is so organized that it is less vulnerable.

Alcoholic Psychoses.—Acute Alcoholism.—The most familiar mental disorder due to alcohol is acute alcoholic intoxication, with weakening of acquired inhibitions and the release of underlying tendencies. In some patients this change reveals a quarrelsome or churlish mood, in others merriment and humor or a sentimental tendency.

Chronic Alcoholism.—The personal deterioration and insidious loss of the finer reactions, which result from chronic alcoholism, are expressed by indifference to the social demands which once evoked response, or by crude, brutal, aggressive behavior. In spite of such serious changes in the ethical sensitiveness, the patient may maintain such a fair exterior and air of plausibility that the degree of deterioration cannot be determined readily in a single interview. Even a patient with mental deterioration, impairment of memory, and marked untruthfulness can sometimes lead the listener to believe that he is the victim of unjust persecution.

Ideas of Infidelity (*Alcoholic Paranoia*).—One of the most common symptoms of the chronic alcoholic is to accuse the husband or wife of infidelity. Periods during which this tendency decreases may alternate with periods of increased suspicion and in the latter the patient may take aggressive action. The marked tendency to jealousy may be interpreted either as a desire to bring an accusation of improper sexual behavior because of the unfavorable influence of alcohol on the sexual activity of the

subject himself; or, more subtly, as the expression of an underlying homosexual trend. A homosexual individual tends to develop alcoholic habits through association with those of the same sex in places of recreation, and by unconsciously trying to dull the conflicts within his own nature. The very homosexual tendency which leads to alcoholism evokes a projection of sexual misconduct on the marital partner.

Delirium Tremens.—At the onset of delirium tremens, objects seem to be not quite stationary, and the patient begins to see things running over his skin and over the bed. In the varied visual hallucinations, a regular panorama may pass before the patient's eyes, and large and small objects may appear in bewildering variety. The usual mood of fear is sometimes replaced by tolerant good humor toward the phantasmagoria. There is tremor of tongue and fingers, rapid pulse, frequently slight fever, coated tongue, and transitory albuminuria. After a day or two of sleeplessness and restlessness, during which the patient is dominated by the hallucinations, is sometimes in a state of panic, and may talk with a muttering difficult to follow, profound sleep ensues. From this the subject wakes clear and collected, bathed in perspiration, and with practically no tremor. When this does not occur, the delirium gradually subsides until at the end of a week normal mental clarity has been recovered. If left alone, particularly under restraint, patients may develop fear which leads to fatal exhaustion. As a rule, recovery is complete, but there is some danger of a residual defect of memory. During the attack tactful distraction and reassurance are necessary, and a continuous warm bath may be given for the restlessness. Paraldehyde and veronal may be used to induce sleep. Liquid food should be given in abundance.

Korsakoff's Psychosis.—In some cases, after the mental confusion and hallucinations of alcoholic delirium have disappeared, there is great difficulty in retaining new impressions. This prevents the patient from recognizing his surroundings and appreciating time. The gap in memory may be filled with fabrications, which are spontaneously described in great detail. This condition is frequently associated with polyneuritis. The prognosis is poor as regards memory, but complete return of memory is still possible if only a brief interval has elapsed since the cessation of delirium.

Acute Alcoholic Hallucinosis.—The condition is much less frequent than is delirium tremens. It is liable to develop in the middle of a debauch; the patient is overcome with fear, hears threatening voices which talk of killing him, and accuse him of gross sexual perversions. A somewhat elaborate series of ideas of persecution may rapidly develop. The patient not rarely flees from the imaginary dangers to the police station or hospital for help. Usually the patient can tell clearly about the threatening voices, but occasionally they may so preoccupy him that he is unable to converse with the physician and lies gazing at the ceiling in an hallucinatory stupor.

This psychosis tends to clear up in a few weeks. The prognosis is somewhat more uncertain than in delirium tremens; in some cases the hallucinations persist and the patient becomes more or less resigned to them; in others, the mental disorder becomes more complicated, the ideas more fantastic, and the syndrome closely resembles that of schizophrenic mental deterioration.

Pathologic Alcoholic Intoxication.—Some individuals are so intolerant of alcohol that they react to very small doses with excitement. In this con-

dition they lose their grasp of the environment and in a state of mental confusion carry out complicated actions, and live through dramatic episodes, in which they are wildly aggressive or defend themselves against imaginary enemies. After the critical sleep which ensues, there is no remembrance or only a very summary remembrance of such incidents. The kinship between this reaction to alcohol and the epileptic constitution may be close.

Affective Disorders (*Manic-depressive Insanity*).—Next to fear, depression is the most common specter of man. It may be slight or pronounced, brief or persistent, without apparent cause, the reaction to some distressing situation with normal physical health, or the accompaniment of some somatic ailment. It is so frequently associated with mental upsets that at one time all so-called insanity was thought to begin with a period of "melancholia." This old term, "melancholia," is best avoided because it has many confusing associations. When the depressed mood is the central factor in a psychosis and is not merely one element in a complicated syndrome, the condition may be called an essential "depression." The patient who at one time has an attack of simple depression, is liable at some other time to have the opposite type of attack, an elated excitement. Since both depression and elation seem to be manifestations of a single type of constitutional instability, and may occur at different times in the same patient, it is useful to designate the condition "manic-depressive insanity" as Kraepelin suggested.

Etiology.—The actual situations which precipitate an attack of manic-depressive insanity do not in themselves seem to be adequate cause for the psychosis. Such a mental change is more than the natural reaction to such misfortunes as loss of money, disappointment in one's career, thwarted love, or bereavement, and yet these factors seem to play a rôle in the immediate production of the depressive or related phase of the condition. That physical ailments are basic etiologic factors has never been definitely proved Correlation of focal infections and the development of the psychosis is the result of uncritical observation, and the suggestion that thyroid instability may evoke the manic-depressive condition has little foundation. It is, therefore, necessary to assume that, in a given individual, affective instability, which may be elicited by a variety of factors, is the fundamental cause. This is the so-called *constitutional factor*. The specific lack of resistance can neither be definitely localized nor formulated in precise physiologic terms, but must be defined as an immunologic quality of the organism at the psychologic level. Such special predisposition is apt to be inherited, and may not be made manifest until some factor such as trauma to the head, an epileptiform attack, incipient general paralysis, a great variety of physical ailments (*e. g.*, influenza, cardiovascular or gastro-intestinal disorder), or some unduly difficult problem precipitates the psychosis.

Symptoms.—It is customary to describe three main forms of the manic-depressive type of reaction—the depressed, the elated or manic, and the "mixed." Patients do not present the reaction of these forms in pure culture, but frequently with symptoms of more complicated psychologic origin. The occurrence of peculiar fantasies and odd behavior complicating the affective type of reaction has its analogue in normal psychology, when imaginative elaboration is used to make tolerable a situation which can only partly be dealt with by the affective mechanism.

Depression of Manic-depressive Type.—In this condition the patient complains of sadness, depression, loss of ambition, loneliness, lack of initiative, a feeling that the house is cold, that things seem different. The mood is usually one of continuous and consistent depression, but there may be occasional unexpected brightness or coyness. The depression may be severe in the morning and disappear entirely as evening approaches. The patient sees the past, present, and future through the distorted medium of a depressed mood. The fact that he is unable to carry out his ordinary tasks is distressing to the patient and the contrast between his condition and that of his normal associates adds to his depression. The face assumes a downcast, wooden expression, the appetite is poor and there is a tendency to constipation; sleep is variable and not refreshing. Agitated patients tend to awaken early in the morning.

Excitement of Manic-depressive Type.—In this form of the psychosis the patient becomes elated, is exuberantly active, and very talkative. As a rule he is clearly oriented and but little subject to hallucinations and delusions. The sense of fitness may be so reduced that speech is guided by no reference to a definite topic or situation, and the stream of talk is deflected by the mere sound of words or casual stimuli. Punning and rhyming are common. The general behavior, like speech, lacks the inhibition which normally represses impulsive, trivial, and primitive reactions. As the familiar scheme of values becomes altered the patient is apt to talk in a very crude and primitive manner about topics which are not normally mentioned, and to indulge in bodily exposure, or to make crude sexual advances. In the characteristic haste there is not time to elaborate accurately any impressions, and there is a tendency to be guided by the imperfect first impression or by some casual similarity. The patient may claim in a fleeting way to see snakes in the electric-light globe or objects on the wall, or to hear conversations, although he has no fixed belief in the reality of these experiences. Because the imagination is lively, there may be great delight in fabrication or dramatization. For instance, a one-sided conversation through the telephone may be held with all appearance of seriousness, and later be referred to as play. Throughout such an attack of excitement the patient may be quite clear as to the nature of the environment and the sequence of time, and may, when the attention can be held for a minute, show that his store of general information is retained. If the condition becomes very severe, however, the sense of time and surroundings may be lost, the various words or phrases spoken seem quite disconnected, and the over-activity consists of incessant, exaggerated, more or less meaningless gestures and aggressive activity. The excitement in rare instances resembles that of toxic delirium. In other cases hallucinations may develop which are clearly related to important topics, to memories of critical experiences, or to personal difficulties of great emotional value. The more prominent such elements are, the less simple and benign the disturbance.

The *physical condition* may remain good during the period of excitement. The patient may present a bright, alert appearance, with sparkling eyes and clear skin, and carry on the extraordinary activity for weeks without showing obvious sign of fatigue in spite of little sleep. For weeks at a time there may be only three or four hours of sleep a night. The appetite is often normal, but may be excessive.

"Mixed Conditions" of Manic-depressive Insanity.—In these conditions

symptoms derived from both the depressed and the elated phase occur simultaneously. For example, depression and inactivity may be associated with a certain pressure of speech and flight of ideas; or elation and mild overactivity may accompany muteness and reduced productivity. These combinations may occur in the course of otherwise typical manic-depressive attacks or they may constitute in themselves the whole attack. Such a "mixed condition" may be followed in the next attack by a typical manic excitement or depression. The mixed conditions are evidence that the mood, the disorder of behavior, and the disorder of thought have a certain independence.

Some patients have a series of attacks, each one composed of a depressed and an elated phase (*folie à double forme*); in other patients depression succeeds elation, and elation depression without any break in the morbid cycle (circular insanity).

Prognosis.—The symptoms outlined above do not seem to be evidence of any specific disease or disorder which can be formulated in simple physiologic or biochemic terms. They are manifestations of a very characteristic mode of reaction which does not, as a rule, leave any definite, permanent, residual effects. Without complications the prognosis is good, but with them it must be modified according to their severity and significance. In so far as eccentricity of behavior, queer ideas, and hallucinations of sight or hearing play a part in the psychosis, the prognosis becomes uncertain; but definite depression or elation with flight of ideas reduces the significance of these more serious symptoms.

The duration of manic-depressive insanity is not dependent on the duration of the physical disorder which may have precipitated it; an infection or other somatic ailment may persist long after the psychosis has disappeared and vice versa. The fact that an associated physical disorder is incurable does not make necessary the assumption that depression will persist. A severe attack of excitement may end within two or three months, while a much less pronounced disturbance often continues for more than a year; so with the duration of a depression. To a certain extent the length of one attack helps in an estimate of the length of subsequent attacks. Gradual subsidence of the disordered mood is more favorable than sudden, unexpected improvement, for the latter change may be transient. An attack may end with the subsidence of the characteristic symptoms, but there is always the possibility that the other phase of the disorder may develop, and that instead of recovering the patient may suffer continuous alternation of the different phases. Here again, previous experience may indicate what is to come. In a few cases the normal equilibrium is not regained even when there have been no complicating factors, and a mild excitement or depression may continue for years or even decades. This persistency is more often associated with mild than with severe conditions. Some patients may become normal for such brief intervals between attacks that rearrangement of their daily life in normal surroundings is hardly worth while. In elderly individuals depression is apt to persist longer than in young patients; and there is always a possibility that, as time passes, the marked emotional strain may lead to vascular changes and cortical degeneration with the common symptoms of organic disease of the brain.

Treatment.—Careful physical examination is essential whether or not the immediate cause of the psychosis seems to be a somatic ailment. Such

simple functions as nutrition, elimination, sleep, and exercise must be regulated. Although the special determinants of the manic-depressive condition are not yet understood, it is possible to study and modify certain factors which precipitate the disturbance; the special stresses of the patient's life should be scrutinized and it is worth while to review intimate problems of his personality with him so that he may deal more efficiently with the issues of life. Such a psychologic review is unwise during the depression or elation, but can profitably be undertaken during the convalescence.

Depressive Conditions.—For several reasons it is advisable to send a patient with the depressed type of manic-depressive insanity to a hospital. It may be much less distressing for him to be associated with other depressed individuals than to be surrounded with the normal cheer, happiness, and activity which contrasts so strikingly with his own mood. Relatives often do not appreciate this, and the patient himself looks forward with depression to the hospital, as to everything else. Relief from care for the daily routine is an advantage to the patient, and the possibility of taking special precautions without the patient's knowledge is a gain. For instance, at home, removal of sharp instruments, medicines, and locks, and barring or guarding of upper windows is noticed and recognized as a precaution against suicide; in the hospital such measures may be taken before the patient arrives and pass unnoticed.

The danger of suicide is seldom fully appreciated by the general practitioner. It is greatest perhaps when the patient talks least about it and the attendant is off his guard. With profound depression and marked lack of initiative it is less than when these symptoms are milder. It is the patient who is beginning to improve who is very apt to attempt suicide successfully.

The daily program should include opportunities for both occupation and recreation, but there must be no attempt to urge on a depressed patient unduly, or to entertain him too vigorously. He should live in a quiet atmosphere of understanding and placid acceptance of his limitations, and be surrounded by a spirit of mild, unaggressive optimism.

It is advisable for the physician to give the patient an opportunity to unburden himself of any topics which he cares spontaneously to discuss, for it may be possible to relieve some of the depression by giving these the proper perspective. Undue urging, on the other hand, involves the danger of bringing up painful memories which may increase the distress.

Manic Excitement.—Treatment of manic excitement at home is rarely possible and requires transformation of the entire house into a hospital. *Intelligent nursing* is the most important therapeutic measure. Great tact is necessary, not so much in meeting difficult situations as in avoiding them. A rigid, tactless nurse may evoke antagonism and irritation which makes the patient extremely difficult to control, while one more tactful may steer him in the desired direction and find outlets for his energy in innocent occupations. As the patient is at all times exuberant, active, aggressive, erotic, talkative, full of plans, and sleepless, the problem of treatment is always difficult. Direction and not restraint is essential, and the atmosphere surrounding the patient must be one of placid understanding.

In the treatment of this type of excitement there is one great resource—to place the patient in a *warm bath* (96°–98° F.), and allow him to spend the better part of the day there splashing about and talking vociferously. If

he is too excited, or refuses to remain in the bath, a warm pack may be applied for two hours. After an interval of one hour this may be repeated or followed by a warm bath. Such treatment reduces the tendency to insomnia and refusal of food. The patient uses up less energy than when he is struggling with attendants in his own room, or playfully destroying the furniture and the walls.

If sleep is seriously deficient, it is wise to administer a hypnotic; paraldehyde (8 c.c. well diluted with water) is the best, but veronal and other preparations may be used.

Schizophrenic Conditions (*Psychoses with Marked Hallucinations and Delusions and Peculiar Disorganization of Thought and Behavior; Dementia Præcox*).—In the somewhat heterogeneous group of the schizophrenic conditions are found the majority of mental patients without obvious organic lesion who accumulate as the chronic inmates of the mental hospitals. Our knowledge of these disorders is very inadequate.

Kahlbaum in 1874, with general paralysis in his mind as a paradigm, emphasized the motor reactions in another group of mental disorders, and outlined what he considered to be a definite clinical entity (catatonia); his pupil, Hecker, outlined the symptom-complex of a disorder (hebephrenia) of adolescent or early adult life which produces rapid and pronounced mental deterioration. Kraepelin in 1893 claimed that these clinical forms were but different manifestations of a disorder which also expressed itself in a special form of dementia in which delusions played a prominent rôle (dementia paranoides). For this underlying disorder he used the term "dementia præcox."

The point of view and the nomenclature of Kraepelin suggest a definite disease, a definite, but obscure morbid process, a relentless evolution. So far the facts do not support this fatalistic view, and it is better to use for this large clinical group Bleuler's term "schizophrenia," rather than the term "dementia præcox" with its dubious associations.

Etiology.—In attempts to discover the cause of schizophrenic conditions, both physical ailments and peculiarities of constitution, habits, experience, and situation of patients have been investigated. It has not been possible to demonstrate any uniform disease process. The onset of schizophrenic symptoms after childbirth and other acute physical stresses has been frequently observed. Some investigators lay emphasis on various physical anomalies, indications of endocrine dysfunction, faulty oral hygiene, gastro-intestinal anomalies, and variations in the blood, but the etiologic rôle of all these factors is not certainly understood. Kahlbaum placed undue weight on the motor symptoms. Mott's claim as to the etiologic rôle of a disturbance of the gonads is not supported by the careful observations of Morse. Dunlap has shown the need of caution in interpreting cortical changes. Meyer and Hoch have shown that the schizophrenic condition arises, as a rule, in patients who, even before the onset of the psychosis, are rather shut-in, mix poorly with their fellows, have feelings of inferiority, compensate for difficulty in the real world by withdrawing to a world of fantasy, and have difficulty in assimilating the demands of the sexual instinct. If the fundamental inadequacy of the patient be well marked, whether it be expressed in terms of difficult adaptation to the environment or in terms of endocrine or other somatic determinants of behavior, the schizophrenic symptoms may develop without any precipitating somatic disorder or unusual environmental strain.

Symptoms.—The onset is usually insidious and may be no more than

the accentuation of long-standing traits and modes of behavior. Sometimes the first symptoms appear after some physical illness, or childbirth, or may follow occupational disappointment, bereavement, a thwarted love affair or even an engagement; often there is no evidence of preceding acute or chronic bodily illness or of undue strain. Frank depression is lacking, as a rule, but a subtle change is manifested by preoccupation, irritability, variability of mood and episodic suspicion. Common early symptoms are difficulty in concentration, inability to continue efficiently the usual work, unaccustomed absorption in religious or other activities, loss of interest in the regular tasks and increased seclusiveness. Even at an early stage the patient may complain of peculiar subjective experiences, mysterious influences, unusual feelings in the head, a sensation that something has snapped or suddenly gone wrong. He may complain of interference with his thoughts or of a feeling of passivity, because his thoughts and impulses do not seem to be part and parcel of the usual personal experiences. A patient may hear peculiar sounds or voices, or receive communications in very special ways. He may have visions at night, may even tell of unusual visual experiences in the day time. There is a tendency to misinterpret the behavior of associates, to see a personal reference in neutral incidents, to read a certain attitude into those with whom the patient has special contact, and to transform the whole environment in the light of suspicions, fears, wishes, or special sensitiveness. In the morbid experiences and ideas, religious and erotic elements play an important rôle. The patient may develop odd ideas about his own body and imagine that all sorts of fantastic changes have taken place in the various organs. Odd dietetic or gymnastic fads are common. Despite these disturbances, the memory and the store of information usually remain intact and the patient can carry out elaborate intellectual processes provided his special emotional sensitiveness is not involved. Such a syndrome is an indication of a serious failure of adaptation to the demands of social life and to the conflicts of human nature. In some cases, the mental distortion cripples the general social and economic efficiency without making life at home impossible, but in others the impulsive behavior, the morbid beliefs, and the disturbed emotional life necessitate hospital care.

Hebephrenia.—The condition described by Hecker as hebephrenia is characterized by instability of mood, exaggeration and superficiality of emotional reaction, absurd fancies, and a mixture of crudity and pretentiousness which produces a caricature of adolescent mentality.

Catatonia.—In Kahlbaum's catatonia, bizarre movements and postures, grimacing, waxy flexibility of the limbs, a negativistic attitude with mutism and general rigidity, refusal of food, maintenance of attitudes, and repetition of special movements during periods of excitement are of diagnostic importance, although they are not pathognomonic. They suggest a serious disorder, but the diagnosis and prognosis depend not on such symptoms, but on the detailed evolution of the case. The symptoms vary at different phases. Stupor associated with other catatonic symptoms may be followed by excitement with impulsive behavior and stereotyped utterances, and later by comparative tranquillity with a fair equilibrium, during which period the patient is sometimes able to take part in social activities without showing more than a few overt peculiarities of behavior, although the morbid attitudes and occasional hallucinations still persist.

Diagnosis.—A central symptom of schizophrenic conditions is the

oddity, the bizarreness of the reactions, the queerness of the intellectual constructions, the bewildering anomalies of the emotional life into which the observer cannot feel himself as he can into the depression of the melancholic or the exuberance of the manic. Schizophrenic disorders may be distinguished from *organic disease of the brain*, because they are characteristically manifested by queer, disconcerting utterances and behavior which seem to be very definitely related to certain topics of great personal significance to the patient. The better retention of the intellectual functions is also a distinguishing feature of schizophrenia.

Prognosis.—The outcome of schizophrenia varies from apparently satisfactory recovery to conditions of profound and permanent mental impairment. In the latter the patient lives an inner life which is difficult to penetrate, loses all interest in the outside world, and completely neglects acquired social habits, even cleanliness and decency. The factors which determine the prognosis are as subtle and as complex as those which lead to the break in adjustment, and the causes of the individual variations of the disorder are not easy to analyze in detail. It cannot be too strongly emphasized, however, that the factor or factors which determine the deterioration are obscure and possibly, in part, to be found in the environment; that the degree of deterioration is very variable; that an apparent deterioration may prove to be transitory and be followed by complete recovery; and that the symptoms which are thought to be the best evidence of deterioration may occur in what proves to be a benign disorder. When the breakdown requires little provocation and seems to be merely the evolution of some constitutional inadequacy, the chance of recovery is extremely poor. If, on the other hand, the symptoms begin acutely after considerable provocation (childbirth, physical trauma, the strain of warfare, an acute situation of thwarted love or ambition) the probability of recovery is much greater. The presence of great emotional turmoil is of better prognostic significance than placid acceptance of hallucinatory and delusional experiences and serious withdrawal of interest from the environment, in the absence of any general excitement.

Treatment.—The object of treatment is to alter the abnormal balance between interest in the world of fantasy and in the environment, and to produce the optimum physical condition. This demands desensitization of the patient to memories of past experiences and situations which have acquired false emotional values, and the promotion of healthy activity and thought so that abnormal habits may be gradually discarded. The hospital provides for this a more neutral atmosphere than the home, with the emotional associations of the latter, and permits continuous observation and treatment, but, unless it is well equipped and has a stimulating therapeutic atmosphere, it may lack the conditions necessary for a helpful daily routine. Opportunity to arouse the latent interest of the patient is essential, and occupational therapy should be used to develop the habit of productive activity. The tasks assigned may vary from simple repetitive procedures to those which utilize special artistic, mechanical, or intellectual skill. In addition to this type of treatment, it is necessary for the physician to *analyze the evolution of the disorder*, with its oddities of behavior and thought, and to study its relation to the life situation of the patient. The gratifying reconstruction of the patient's life which in a few instances is possible and permits resumption of previous occupations, more than outweighs the

difficulty of the task. In caring for the *physical needs* of the patient, attention must be paid to oral hygiene and to the gastro-intestinal tract. In extreme conditions of negativism and stupor the patient may refuse all food, so that prolonged tube-feeding is necessary. Sufficient exercise and interesting recreation in the open air must be included in the daily routine. Hydrotherapy often proves helpful. It is important to remember that many reactions which are attributed to the inevitable progress of the disorder may possibly be due to faulty treatment, and that the artefacts caused by the empty routine life in huge institutions must not receive too much weight in the formulation of the fundamental nature of the disorder.

Paranoic Conditions.—Separated from the large group of patients with well-marked delusions is a small group of those with delusional misinterpretations unaccompanied by the strange disturbances of thought and behavior characteristic of schizophrenic conditions. Such patients maintain in a surprising degree the logical structure of thought, which contrasts strikingly with the content of the delusional beliefs. Paranoia may disturb ordinary social intercourse very little, and even in a prolonged interview the patient may fail to reveal any deviation from normal. He may not admit that he has peculiar experiences, and even when the physician knows that he is particularly sensitive to certain topics, the patient may refuse to give any indication of his real attitude. Consequently, it is often incidentally or under special circumstances that the physician is able to obtain from the patient a full account of the ideas which dominate him. Some patients, however, are not so reticent, and on the first opportunity elaborate their ideas in the greatest detail. In some cases the morbid attitude is based on a real grievance; in others the preoccupation springs from the realm of subconscious desires.

When there is a real, specific grievance and all efforts to get redress have failed, the inability to do so and the lack of appreciation of the point of view of others lead the patient to attribute the indifference or antagonism of others to all sorts of unworthy and complicated motives. He may even see in the simplest behavior of his fellows indication of a wide-spread conspiracy against him. Such misinterpretation covers indifferent matter in the daily papers, the incidental and meaningless trifles of the every-day remarks and actions of neighbors, the significance of sermons. The undue insistence on whatever right is on the patient's side is allowed to interfere with the entire social adaptation.

The preoccupation which springs from subconscious desire may concern love, power, or prestige. The patient sometimes believes that an individual is in love with him, and that certain hostile influences interfere with the whole experience and ruin his life; or there may be the delusion that he is a person of very great value, with special literary, artistic, or scientific ability, and that hostile influences thwart him and hide his native endowment. Such beliefs are tenaciously retained, and modified only with extreme difficulty. There is no withdrawal from reality, but rather a desire to wrest satisfaction from a reality on which he wishes to impose his point of view. This produces not only bitterness, but aggressiveness, which makes the individual so determined to get satisfaction in the real world that he frequently takes drastic steps to this end. Many sudden assaults are explained on this basis, and many murders have been committed by patients under the influence of such ideas. It is important, therefore, to understand

the delusions of the aggressive paranoic thoroughly, and to keep him under strict supervision.

Conditions of Mental Defect.—In certain patients a mental defect, which is either congenital or acquired soon after birth, causes the principal difficulty in adaptation. The abnormality may be recognized very early by the mother when the infant fails to reach out and grasp objects, seems less alert and observant than normal, or is unduly restless or difficult to manage, but it is frequently not observed until there is obvious delay in learning to sit up, stand, walk, or talk, or even until accurate comparison with other children in the standardized environment of the school reveals the deficiency. Before the introduction of standard tests and their employment in schools and in the army, the mentally defective individuals who received most notice were those whom special traits or criminal tendencies made conspicuous. The impression that all mentally defective individuals have criminal tendencies, a poor heredity, and lack of response to ameliorating influences has been modified by demonstration of the fact that a large number of people with subnormal mental equipment are docile, industrious, and have no special tendency to delinquency. These individuals can perform simple routine work, and become a modest economic asset.

Mentally deficient children find particular difficulty in assimilating the material taught in ordinary schools, and in adapting themselves to their schoolmates. They may lag in class, be teased and made a butt of, and are always at the end of the procession. Because they find little pleasure in chronic failure, they are especially liable to play truant, or turn to undesirable companions who may exploit their docility and lack of keenness. In this way, a backward child often learns bad habits, is taught to steal, or to indulge in various sexual activities. If the mental defect is very marked, the school authorities must recognize it, but when it is only slight, no allowance may be made for the lack of capacity, and failure evokes only the discipline suited to normal children. The modified Binet-Simon tests provide a practical means of determining the degree of abnormality in children of school age.

At the end of the school period the mental defect may show itself in the inability to perform any but simple routine tasks or by failure to maintain good conduct. The limited grasp of broader relations, the lack of capacity to become keenly interested in attractive pursuits, and perhaps a sense of inferiority make the mentally defective individual liable to be guided by the impulse of the moment and to succumb to the temptations (especially alcoholism and sexual indulgence), which modern civilization offers in profusion. In a certain number of patients the poor intelligence is associated with abnormal emotions and instincts, the tendency to be turbulent, aggressive, irritable, or to indulge in sexual cravings, sometimes of a perverse nature. Some are cruel, destructive, set fire to buildings, take morbid pleasure in tormenting animals, or teasing weaker children. Standard "performance tests" may be used to determine the degree of deficiency in adults; they test the ability to meet a definite situation rather than verbal skill.

Diagnosis.—The diagnosis of mental defect depends on the response to tests which have been found to measure the capacity of normal individuals and also, as Fernald has emphasized, on the physical status, the family

history, the personal and developmental history, the school progress, the result of examination in school subjects, the amount of practical knowledge and general information, the social history and reactions, the economic efficiency, and the moral reactions. Early recognition of mental defect is very important if the subnormal child is to receive training which will render him useful and happy, and if his normal associates are to be permitted to advance with suitable rapidity. The mentally defective have been classified according to the severity of the mental defect as *idiots*, *imbeciles*, and *morons*. Between the moron and the normal individual is a borderline group of dull individuals, who will be thought mentally defective by some observers, low normal by others.

Prognosis.—The career of the mentally defective may be smooth and uneventful if circumstances are favorable, if the patient be properly supervised, and if other factors in his personality do not make treatment unduly difficult.

Treatment.—Since a mentally defective child cannot grasp complex abstract ideas, his training must be largely mechanical. If the defect is slight, he may drift along in school with his brighter companions; under these conditions he requires special attention to prevent undue emphasis on his inferiority. For children with marked defect, the best training can only be provided in institutions where special stress is laid on manual skill, and where the patient is not handicapped by standards quite disproportionate to his ability.

Conditions of Mental Instability (*Psychopathic Personality, Constitutional Psychopathic Inferiority*).—The intellectual functions are merely one aspect of the adaptive functions of the personality, and an individual may be constitutionally defective in regard to other equally important aspects. There may be undue, disturbing prominence of instinctive demands; perverse instinctive tendencies; peculiar lack of responsiveness to ethical standards with a consequent disconcerting tendency to lie and steal; or lack of the stability and continuity of motives which are so helpful for a productive life. An individual may be subject to moods of unrest, of gradual or acute onset, which make him suddenly interrupt a situation which appears well established, and start off on a fresh trail even when prudence renders such behavior quite undesirable. These constitutional deficiencies sometimes favor development of alcoholism or a generally ill-regulated life, or allow outbursts of ill-balanced emotional expression (rage, jealousy, suspicion).

The term "constitutional psychopathic inferiority" may be applied to the large and rather heterogeneous group of such conditions. It has not as strict a connotation as the terms "hysteria" and "schizophrenia." In one sense it may be applied to most functional mental disorders, for in the manic-depressive, the schizophrenic, the hysterical, and the obsessive individual, the breakdown is very largely dependent on some constitutional quality. The reaction peculiar to each of these groups is, however, sufficiently specific to warrant a special designation for each. In individuals with constitutional psychopathic inferiority there is no one specific type, but the greatest diversity of endowment. Many get along without special incident so long as the situation is favorable and makes no great demands, but any special situation may reveal the peculiar vulnerability. Patients of this type, if imprisoned, not infrequently develop a rather special mental

disorder ("prison psychosis"), with symptoms closely allied to those of certain hysterical or schizophrenic conditions.

The physician must consider each case as a special problem of human adaptation, and endeavor to understand how far the clinical picture is intelligible in the light of the personal constitution of the patient, his past experiences, his present physical condition, and his environment. The general principles of treatment of these acute episodes are the same as in other conditions of excitement, depression, or misinterpretation. In outlining the future of the patient, the physician must keep in mind the special constitutional limitations, the type of situation liable to be dangerous, and the sources from which the patient can obtain safeguards and assistance. This requires an understanding of the opportunities afforded by the community for stimulating and reinforcing valuable mental functions. It is wise to utilize contact with the family, with the church, with groups of fellow-workers or social organizations united by some common cultural or recreational interest.

The Psychopathology of Childhood.—Psychiatry is reaching out to include all those health problems which are related to the instinctive, emotional, and personal forces of the individual. The acceptance of this point of view by the medical profession increases the possibility of its usefulness to the community, and may lead the general practitioner to take a keen interest in the early stages of human maladjustments, and to provide suitable early treatment. Health officers may also come to be interested in the environmental factors which place special strain on the personality, and to think in terms of mental as well as of physical prophylaxis. The progress of psychiatry and its orientation in the direction of early care and prophylaxis lead to special emphasis on the formative period of life when the personality is being molded favorably or unfavorably, is being unfortunately sensitized or fortunately immunized, and when the individual is acquiring his scheme of values and his habits of adaptation to the problems that confront him.

Even in childhood there are many difficulties of adaptation which are manifested in various ways. The physician is too apt to ignore altogether the personality of the child and its problems, and to limit his attention to the physical condition. A child may be moody, have tantrums, be unhealthily dependent on or antagonistic to the parent, may show jealousy and cruelty, may pilfer and fabricate, may explore tentatively the sex field, may indulge in wandering episodes, while the perplexed physician may employ no therapy except regulation of nutrition and sleep. When the parent asks a physician about such habits as thumb-sucking, capriciousness with regard to diet, night-terrors, or masturbation, the physician is apt to base his answer on vague impressions and his intuitive grasp of the situation, although adequate treatment requires the same methodical examination and the same accurately controlled observation as do problems of nutrition and infection. Nocturnal enuresis may be a source of organic satisfaction to the child, or may be connected with his longings for the affectionate care of the mother. Tantrums may be a function of the personality of the mother as well as of the nervous system of the child. Disturbed behavior of various kinds may depend on the jealousy aroused by the advent of a younger child, on feelings of inferiority, or on vague disturbing ruminations over sexual problems. The influence of comrades and of chance experiences

may be very great, especially in an imaginative child. Parents frequently have little inkling of the complex ruminations and the mental attitudes concealed beneath the ordinary behavior of their children. The physician who understands the rôle played by these factors in the disorders of the child may incidentally do much to develop, in a healthy way, the personality of the parent.

C. Macfie Campbell.

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